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**published in**

European Journal of Organic Chemistry  
2019

**DOI (link to publisher)**

[10.1002/ejoc.201900399](https://doi.org/10.1002/ejoc.201900399)

**document version**

Publisher's PDF, also known as Version of record

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**citation for published version (APA)**

van der Heijden, G., van Schaik, T. B., Mouarrawis, V., de Wit, M. J. M., Velde, C. M. L. V., Ruijter, E., & Orru, R. V. A. (2019). Efficient Diastereoselective Three-Component Synthesis of Pipecolic Amides. *European Journal of Organic Chemistry*, 2019(31-32), 5313-5325. <https://doi.org/10.1002/ejoc.201900399>

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## Multicomponent Reactions

Efficient Diastereoselective Three-Component Synthesis of  
Pipelic Amides

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Romano V. A. Orru<sup>\*,[a]</sup>

**Abstract:** An efficient Ugi-type three-component reaction (U-3CR) for the synthesis of pipelic amides is reported. The U-3CR between electronically diverse isocyanides, carboxylic acids and 4-substituted  $\Delta^1$ -piperideines proceeds in a highly diastereoselective fashion. The  $\Delta^1$ -piperideines are obtained by NCS-mediated oxidation of the corresponding 4-substituted

piperidines, which in turn are generated by an efficient two-step procedure involving the alkylation of 4-picoline and subsequent catalytic hydrogenation of the pyridine ring. We demonstrate the utility of this U-3CR, in combination with the convertible isocyanide 2-bromo-6-isocyanopyridine, in the synthesis of the anticoagulant argatroban.

## Introduction

In the past decades, isocyanide-based multicomponent reactions (IMCRs) have proven their value as useful tools for the generation of structurally diverse compound libraries.<sup>[1–3]</sup> The products resulting from these reactions generally feature considerable molecular complexity, as well as one or more new stereocenters. An important advance in the field of IMCRs is the development of methods to gain stereocontrol with the use of cleverly designed (organo)catalysts.<sup>[4–8]</sup> For one of the most widely used IMCRs, the Ugi four-component reaction (U-4CR), no general catalytic method was available until very recently.<sup>[9]</sup> An alternative approach to control the stereochemistry of the Ugi reaction is to use chiral starting materials. Unfortunately, the diastereoselectivity in Ugi reactions is generally very poor, especially for chiral isocyanides and carboxylic acids.<sup>[10]</sup> Moreover, aldehyde inputs have similar problems with the additional disadvantage that the  $\alpha$ -carbon easily undergoes racemization (or epimerization).<sup>[11]</sup> However, the combination of two different functional groups in a single (chiral) reactant provides much better stereocontrol. This has especially been demonstrated in the formation of (macro)cycles.<sup>[12–14]</sup> In addition, chiral amine and imine inputs also typically show reasonable induction in the U-4CR.<sup>[15–19]</sup>

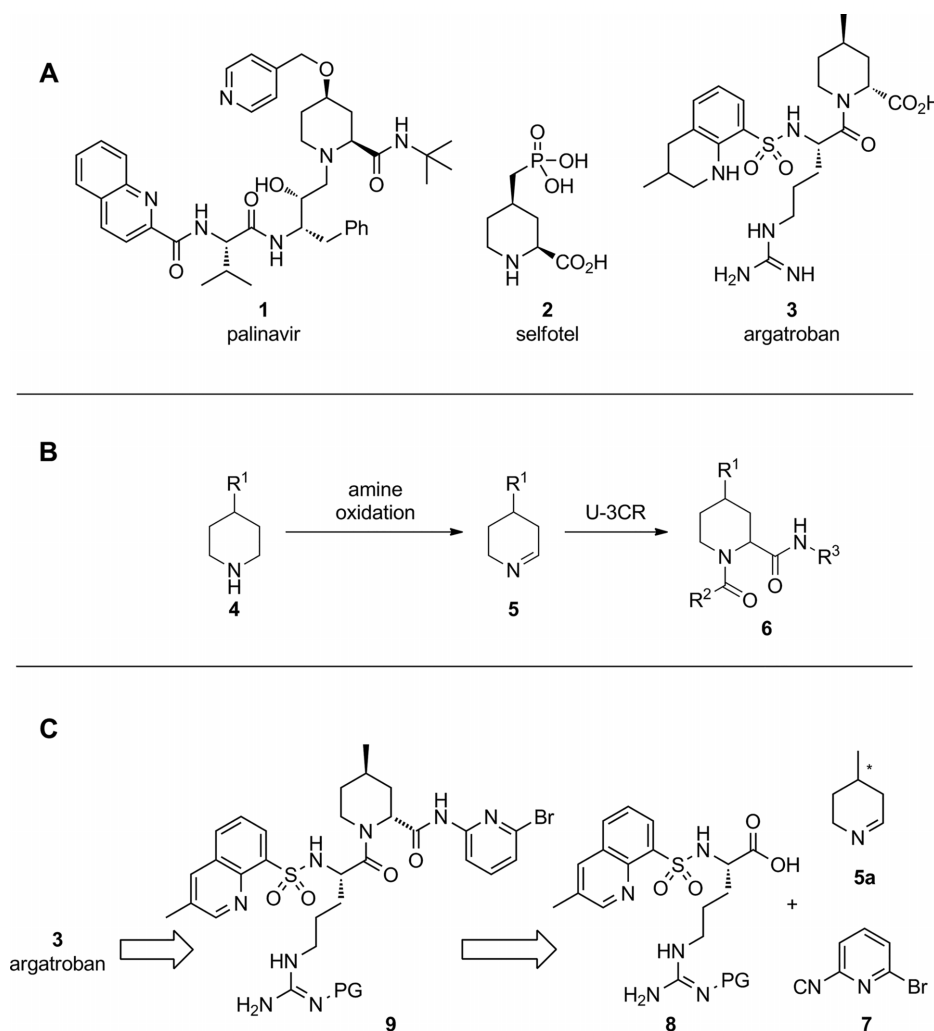
In the past, we reported a highly diastereoselective Ugi three-component reaction (U-3CR) using optically pure 3,4-*cis*-substituted bicyclic 1-pyrrolines for the synthesis of prolyl peptides.<sup>[15]</sup> The diastereoselectivity arises from the steric bulk present in the 1-pyrroline skeleton. This methodology provides access to medicinally relevant prolyl peptides, including the hepatitis C virus NS3 protease inhibitor telaprevir.<sup>[16]</sup> Prolyl peptides are desirable building blocks for medicinal chemistry due to the high occurrence of proline in proteins and oligopeptides. Moreover, amides of the structural homologs of proline, pipelic acid, are common structural motifs in bioactive compounds.<sup>[17–19]</sup> Especially 4-substituted pipelic acid derivatives are an important class of compounds. A large subset of this class consists of bioactive 2,4-*cis*-substituted pipelic amides or acids, such as the potent HIV inhibitor palanivir<sup>[20]</sup> and the NMDA antagonist selfotel<sup>[21,22]</sup> (Scheme 1A, 1 and 2, respectively). Additionally, 2,4-*trans*-pipelic acid derivatives are key motifs in for example antitumor agents and the thrombin inhibitor argatroban (3).<sup>[23]</sup>

According to the literature  $\Delta^1$ -piperideines (5) as well as other cyclic imines are good substrates for IMCR chemistry, e.g. for the synthesis of pipelic acids<sup>[24]</sup> and acyldepsipeptide antibiotics.<sup>[25,26]</sup> Furthermore, El Kaïm and co-workers have shown that 4-benzyl  $\Delta^1$ -piperideine is a good substrate for the Ugi-Smiles reaction.<sup>[27]</sup> Since 2,4-pipelic amides are highly valuable structural motifs, we became interested in the generality of  $\Delta^1$ -piperideines (5) as inputs for the U-3CR (Scheme 1B). Moreover, we envisioned a possible application in the synthesis of argatroban (3). Argatroban is an important therapeutic anticoagulant that directly inhibits the thrombin enzyme, which is responsible for the blood clotting in thrombosis.<sup>[28]</sup> The drug is mainly administered to patients with a history of coronary artery disease (CAD) or stroke, when the conventional antithrombotic drug heparin results in heparin-induced thrombocytopenia (HIT) or platelet deficiency.<sup>[29]</sup> Scheme 1C depicts our retro-

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Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under <https://doi.org/10.1002/ejoc.201900399>.



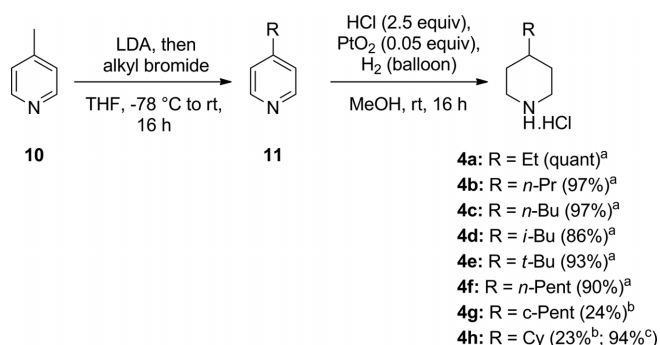
Scheme 1. **A:** Bioactive 4-substituted piperidic acid derivatives. **B:** our synthetic approach toward 2,4-disubstituted piperidic amides (**6**). **C:** Retrosynthetic plan for argatroban (**3**) using the U-3CR approach and convertible isocyanide **7**.

synthetic plan for argatroban, which requires straightforward access to  $\Delta^1$ -piperidines **5** and high diastereoselectivity in the U-3CR for piperidic amides **6**. This, in combination with the use of our universal convertible isocyanide, 2-bromo-6-isocyanopyridine (**7**),<sup>[30]</sup> would result in a highly convergent and very short synthesis of argatroban (**3**).

## Results and Discussion

Since only a handful of different 4-substituted piperidines (**4**) is commercially available, we decided to prepare a considerable set of them ourselves. Initially, we tried to synthesize them via a Wittig reaction of *N*-Cbz piperidone and different alkyltriphenylphosphonium halides followed by catalytic hydrogenation of the resulting alkenes. However, the desired 4-substituted piperidines were obtained in rather modest overall yields (>45 %). We therefore developed an alternative strategy involving lithiation and alkylation of 4-picoline (**10**)<sup>[31,32]</sup> with different alkyl bromides followed by catalytic hydrogenation of the resulting

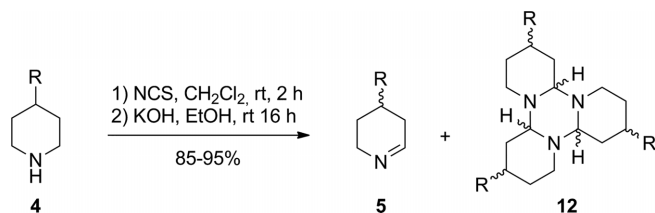
4-alkyl-pyridines **11** over  $\text{PtO}_2$  (Scheme 2).<sup>[33,34]</sup> The alkylation proceeded very efficiently with primary and secondary alkyl bromides to produce the corresponding 4-alkyl pyridines **11** in



Scheme 2. Synthesis of 4-alkylpiperidines **4a–j** from 4-picoline **10**.<sup>[a]</sup> Isolated yields over 2 steps.<sup>[b]</sup> Lower overall yield is due to less efficient double alkylation, the hydrogenation proceeds in all cases in near quantitative yield.<sup>[c]</sup> 4-phenylpyridine could also be used as the starting material in the  $\text{PtO}_2$ -reduction step generating **4h** in 94 % isolated yield.

high yields. The double alkylation with 1,3-dibromopropane and 1,4-dibromobutane using two equivalents of LDA proved successful as well, directly providing the corresponding 4-cyclopentyl- and 4-cyclohexylpyridines. The subsequent hydrogenation of **11** was performed with  $\text{PtO}_2$  as catalyst in the presence of HCl to obtain the desired **4a–h** as odorless HCl salts (a significant advantage compared to the foul smelling free base liquids resulting from the Wittig strategy). Reduction of pyridines is generally performed under elevated hydrogen pressure and reaction temperature, however we discovered that atmospheric hydrogen pressure at room temperature worked equally efficient to provide piperidinium salts **4a–h** in near quantitative yields. Interestingly, the use of 4-phenylpyridine as the starting material for the hydrogenation also provided 4-cyclohexyl piperidine **4h** in similar yield through reduction of the conjugated phenyl ring.<sup>[35]</sup>

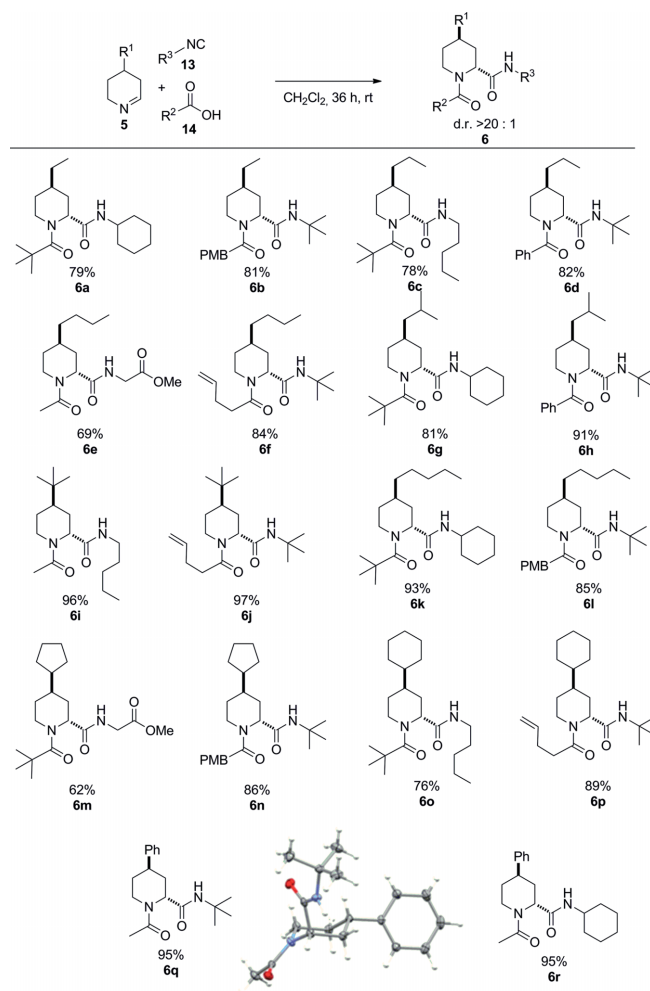
With the 4-alkylpiperidines **4** in hand we synthesized the corresponding (racemic)  $\Delta^1$ -piperideines **5** by NCS-mediated chlorination followed by HCl elimination using ethanolic KOH (Scheme 3).<sup>[36]</sup>  $^1\text{H}$  NMR analysis indicated that the imines were not stable and rapidly formed diastereomeric mixtures of trimers (**12**), which made it difficult to assess the kinetics of the process. To validate if these trimers would still be reactive inputs for the U-3CR, we reacted the obtained mixtures of racemic imines **5** and trimers **12** with a set of different isocyanides (**13**) and carboxylic acids (**14**, Scheme 4).



Scheme 3. Synthesis of racemic  $\Delta^1$ -piperideines **5** and formation of trimers **12**.

To our delight, the corresponding pipecolic amides **6** were obtained in generally excellent yields, indicating that the trimerization is reversible under the reaction conditions. In addition, the pipecolic amides **6** were obtained as single diastereomers, regardless of the size of the alkyl group on the piperidine ring. X-ray crystallographic analysis of compound **6q** confirmed the expected 2,4-*trans*-configuration of the pipecolic amides (see Scheme 4 and the Supporting Information). All other pipecolic amides **6** were assigned the same 2,4-*trans*-configuration by similarity and comparison of  $^1\text{H}$  NMR coupling constants.

The scope of the reaction is very broad in terms of both the isocyanide and carboxylic acid inputs. Both primary, secondary and tertiary aliphatic isocyanides yield the corresponding pipecolic amides **6** in decent isolated yields. This includes isocyanides bearing a strongly electron withdrawing  $\alpha$ -ester moiety (the  $\alpha$ -acidic methyl isocyanoacetate) that give the pipecolic amide products **6e** and **6m**, albeit in slightly lower yields (69 % and 62 %, respectively) compared to the other isocyanide inputs (76–97 %). The carboxylic acid component can be varied widely as well. We employed acetic and pivalic acid giving the corresponding pipecolic amides in good to excellent yields.

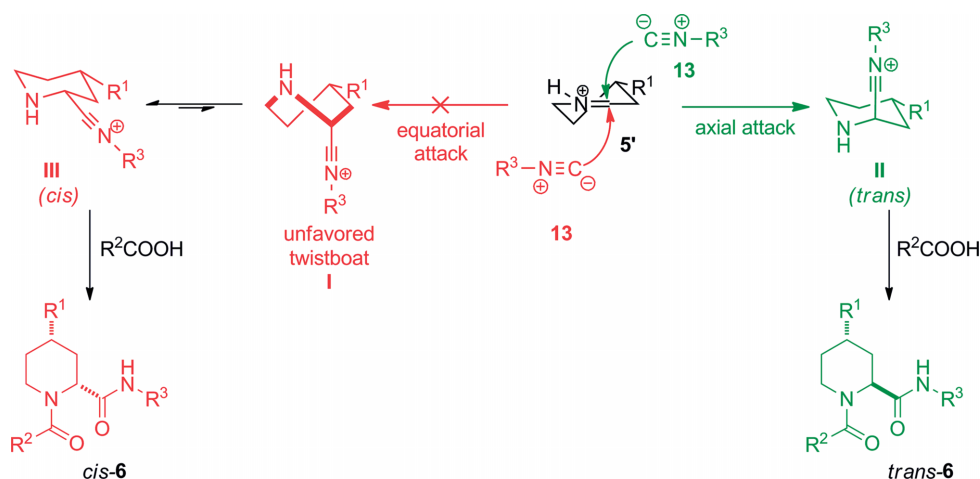


Scheme 4. The scope of the diastereoselective U-3CR towards pipecolic amides **6** and the crystal X-ray structure of compound **6q** with displacement ellipsoids drawn at 50 % probability level.

Even carboxylic acids functionalized with a double bond result efficiently in the pipecolic amides **6f**, **6j**, and **6p**. Also, carboxylic acids with  $\text{R}^2 = \text{aromatic (Ph)}$  or benzylic (PMB) are well tolerated in our three-component reaction. The more congested pivalic acid proved to be an advantageous input for NMR analysis. Most U-3CR products appear as rotamers in the NMR spectra due to hindered rotation of the tertiary amide bond. The steric bulk of the *t*Bu group strongly disfavors one of the possible amide conformations, which greatly simplifies the NMR analysis.

The diastereoselectivity of the U-3CR is determined by the attack of the isocyanide on the charged iminium species. Although nucleophilic attack of the isocyanide from the top face is less hindered due the neighboring equatorial H-atom, this can hardly account for the complete *trans* selectivity observed. However, the observed selectivity can be satisfyingly rationalized by the Fürst-Plattner rules (Scheme 5).<sup>[37]</sup> The initial  $\Delta^1$ -piperideines will, after protonation by the carboxylic acid, most likely adopt the preferred half-chair conformation **5'** with the alkyl substituent positioned pseudo-equatorially.

Nucleophilic attack of the isocyanide (**13**) may then come from the bottom face (equatorial attack, in red), leading to an

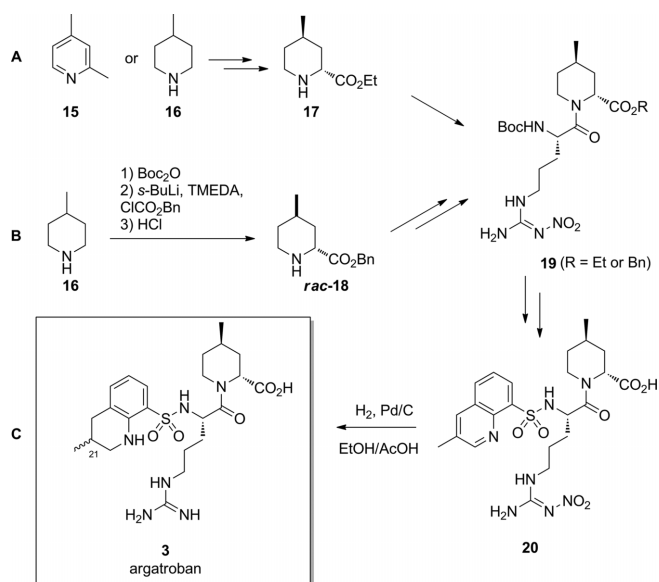


Scheme 5. The proposed mechanism of isocyanide attack on the protonated  $\Delta^1$ -piperideines **5'** leading to diastereoselective formation of *trans*-pipecolic amides **6**.

disfavored twist-boat conformation **I**, or from the top face (axial attack, in green), leading directly to a more favorable chair conformation (**II**). Consequently, the kinetic barrier for an axial attack is much lower than for an equatorial attack, providing exclusively the *trans*-product.<sup>[38,39]</sup>

With the broad scope of the U-3CR and selective formation of the 2,4-*trans* configured pipecolic amides **6** in hand, we envisioned a strategy for the total synthesis of argatroban (**3**). Argatroban (**3**) contains four stereocenters, of which the stereochemistry of the 2,4-disubstituted pipecolic amide and the arginine moiety are defined. Two rather similar approaches for the synthesis of **3** have been reported.<sup>[40,41]</sup> The first approach, developed by the Mitsubishi corporation, utilizes optically pure ethyl (2*R*,4*R*)-4-methyl-piperidine-2-carboxylate (Scheme 6A, **17**) obtained from **15** or **16**. After optical resolution by crystallization with *l*-tartaric acid, a lengthy linear sequence of standard protection/deprotection and peptide coupling reactions gave argatroban (**3**).<sup>[40]</sup> Later, Cossy and Bellotti reported an improved synthesis following a similar strategy (Scheme 6B).<sup>[41]</sup> To avoid the troublesome enantioselective synthesis of pipecolic ester **17** they used the readily accessible racemic pipecolic ester *rac*-**18**, which was prepared by  $\alpha$ -lithiation of *N*-Boc-4-methylpiperidine. The resulting 2-lithiated species was quenched with benzyl chloroformate to obtain the corresponding amino ester with high diastereoselectivity in favor of the *trans*-diastereomer (up to 95:5).<sup>[42]</sup> Subsequent coupling of **18** to *N* $\omega$ -nitro-*l*-arginine and separation of the diastereomers by flash chromatography gave optically pure **19**. Finally, the synthesis of **3** was completed in a similar fashion as the Mitsubishi synthesis. It should be noted that commercial argatroban (**3**) is administered as a 64:36 mixture of the 21-(*R*)- and 21-(*S*) epimers (at the 3-methyltetrahydroquinoline moiety), because the C21 stereocenter is generated in a poorly selective final catalytic hydrogenation step of the quinoline ring (Scheme 6C).<sup>[43]</sup>

Our retrosynthetic analysis (Scheme 1C) shows that next to  $\Delta^1$ -piperideine **5a**, the functionalized and protected arginine derivative **8** is required. Furthermore, our U-3CR strategy takes advantage of a convertible isocyanide **7** as a starting material

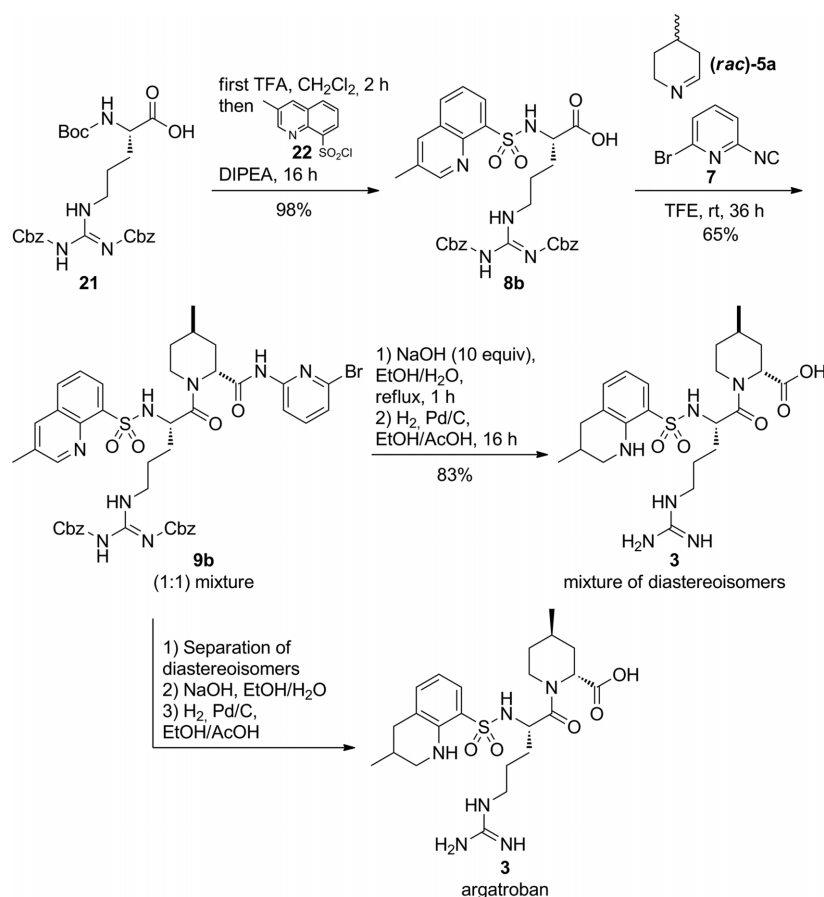


Scheme 6. **A**: The Mitsubishi synthesis of argatroban (**3**).<sup>[40]</sup> **B**: The Cossy and Belotti synthesis of argatroban (**3**).<sup>[41]</sup> **C**: Commercial C21 hydrogenation of the quinolone ring.<sup>[43]</sup>

resulting in the secondary amide **9** that should undergo selective hydrolysis to the corresponding carboxylic acid. Recently, we developed 2-bromo-6-isocyanopyridine (**7**) as a universal convertible isocyanide for selective post-transformations of Ugi and Passerini products under mild acidic or alkaline conditions.<sup>[30]</sup>

Piperideine **5a** was obtained from commercial **16** by the NCS-mediated chlorination followed by HCl elimination described in Scheme 3. For the  $NO_2$ -protected quinolyl sulfonamide **8a** (PG =  $NO_2$ ) we initially envisioned to use (like Cossy and Belotti) *N* $\omega$ -nitro-*l*-arginine as the functionalized carboxylic acid input for the U-3CR. This should have several advantages. Firstly, the nitro group is much smaller than most other protection groups, improving the overall atom economy. Secondly, the nitro group is one of the strongest electron-withdrawing groups, which completely deactivates the guanidine, resulting





Scheme 7. Synthesis of argatroban using the diastereoselective U-3CR for pipecolic amides.

in higher yields in the U-3CR. Finally, the nitro group can be removed in the final reaction step simultaneously with the reduction of the quinolone ring. An initial test of the U-3CR/hydrolysis route using **5a**, *N*<sub>ω</sub>-nitro-*L*-arginine and our convertible isocyanide **7** indicated that the nitroguanidine group of **9a** (PG = NO<sub>2</sub>) degrades during the hydrolysis step, giving the corresponding primary amine or urea derivatives (as determined by <sup>1</sup>H NMR and HPLC-MS analysis). Therefore, we favored the double Cbz, mono Boc protected arginine **21** as input (Scheme 7), which can also be removed in the final hydrogenation reaction. Thus, the Boc group of **21** was removed by treatment with TFA and the resulting amine was sulfonylated with 3-methyl-8-quinolinesulfonyl chloride (**22**) in the presence of DIPEA to furnish double Cbz-protected carboxylic acid **8b** in nearly quantitative yield. Our diastereoselective three-component pipecolic amide synthesis using **8b** in combination with convertible isocyanide **7** and racemic imine **5a**<sup>[44]</sup> gave Cbz-protected U-3CR product **9b** in 65 % yield. This nicely demonstrates that our three-component reaction towards pipecolic amides is really robust tolerating even highly functionalized carboxylic acids as well as the less nucleophilic heteroaromatic isocyanides as inputs. The activated amide of **9b**, resulting from the 2-bromo-6-isocyanopyridine **7**, was hydrolyzed with aqueous NaOH at elevated temperature. Interestingly, the Cbz groups appear sensitive to these reaction conditions, resulting in the quantitative removal of one of the Cbz groups and partial

removal of the other. Finally, the quinolone ring was reduced, and the remaining Cbz-group was removed by catalytic hydrogenation (H<sub>2</sub>, Pd/C) to afford argatroban (**3**) in 83 % yield as a mixture of two diastereoisomers. In order to obtain the (*L,R,R*)-diastereoisomer of **3**, the 1:1 mixture of the (*L,S,S*)- and (*L,R,R*)-Ugi diastereoisomers **9b** was separated by supercritical fluid chromatography (SFC).<sup>[45]</sup> The desired diastereomer was converted under similar conditions to obtain (*L,R,R*)-**3** as a 36:64 mixture of epimers at the quinolone C21 stereocenter.<sup>[46]</sup>

## Conclusions

In conclusion, we have developed an efficient and highly diastereoselective U-3CR with Δ<sup>1</sup>-piperidine derivatives as versatile inputs. The reaction tolerates chemically diverse isocyanides and carboxylic acids leading to a wide variety of medicinally interesting pipecolic amides. The desired 4-substituted Δ<sup>1</sup>-piperidine derivatives were made by a simple chemical oxidation of the corresponding piperidines. These piperidines were synthesized by an alkylation of 4-picoline followed by hydrogenation of the pyridine ring with hydrogen and catalytic PtO<sub>2</sub> in the presence of HCl. As a demonstration of the potential of the U-3CR, we used our methodology in combination with our recently developed convertible isocyanide 2-bromo-6-isocyanopyridine for a very short synthesis of the anticoagulant argatroban (**3**).

## Experimental Section

**General Remarks:** Unless stated otherwise, all solvents and commercially available reagents were used as purchased. All reactions were performed under air, unless stated otherwise. Infrared (IR) spectra were recorded neat using a Shimadzu FTIR-8400s spectrophotometer and wavelengths are reported in  $\text{cm}^{-1}$ . Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 500 (125.78 MHz for  $^{13}\text{C}$ ) or Bruker Avance 400 (100.62 MHz for  $^{13}\text{C}$ ) using the residual solvent as internal ( $^1\text{H}$ :  $\delta$  7.26 ppm,  $^{13}\text{C}\{^1\text{H}\}$ :  $\delta$  77.00 ppm for  $\text{CDCl}_3$ ,  $^1\text{H}$ :  $\delta$  2.50 ppm,  $^{13}\text{C}\{^1\text{H}\}$ :  $\delta$  39.52 ppm for  $[\text{D}_6]\text{DMSO}$  and  $^1\text{H}$ :  $\delta$  3.31 ppm,  $^{13}\text{C}\{^1\text{H}\}$ :  $\delta$  49.00 ppm for  $[\text{D}_4]\text{MeOD}$ ). Chemical shifts ( $\delta$ ) are given in ppm and coupling constants ( $J$ ) are quoted in **Hertz** (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), bs (broad signal) and m (multiplet) or combinations thereof. Chiral HPLC was recorded using a LC10VP with a SCL-10A VP system controller, LC-10AT VP liquid chromatograph, SPD-M10A VP diode array detector and CTO-10AC VP column oven from Shimadzu. Data was processed using Shimadzu Labsolutions. Semi-preparative reverse phase HPLC was recorded using a LC20 with a CBM-20A communications bus module, LC-20AT liquid chromatograph, SPD-M20A diode array detector, SIL-20A auto sampler, CTO-20AC column oven and a FRC-10A fraction collector from Shimadzu. Melting points were recorded on a Büchi M-565 melting point apparatus and are uncorrected. Electrospray ionization (ESI) high-resolution mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Flash chromatography was performed on Silicycle Silia-P Flash Silica Gel (particle size 40–63  $\mu\text{m}$ , pore diameter 60 Å) using the indicated eluent. Thin Layer Chromatography (TLC) was performed using TLC plates from Merck ( $\text{SiO}_2$ , Kieselgel 60 F254 neutral, on aluminium with fluorescence indicator) and compounds were visualized by UV detection (254 nm) and  $\text{KMnO}_4$  stain. Protected arginine 21 ( $\text{Boc-Arg}(\text{Cbz})_2\text{-OH}$ ), 3-methylquinoline-8-sulfonyl chloride (22), 4-methylpiperidine (16), 4-phenylpiperidine as well as pyridines 11a and 11e are commercially available and were used as purchased.

### Synthesis of 4-Substituted Piperidinium Salts (4)

**General Procedure I. Synthesis of 4-Alkylpyridines (11):** A flame dried three-neck round-bottomed flask under  $\text{N}_2$  atmosphere was charged with a solution of diisopropylamine (5.0 mL, 35.7 mmol, 1.55 equiv.) in anhydrous THF (100 mL). The reaction mixture was cooled to  $-78^\circ\text{C}$  and a solution of *n*-butyllithium (1.6 M in hexanes, 21.6 mL, 34.5 mmol, 1.5 equiv.) was added dropwise. After 10 min, the solution was warmed to  $0^\circ\text{C}$  and stirred for another 20 min. The solution was cooled again to  $-78^\circ\text{C}$  and 4-picoline (2.24 mL, 23 mmol, 1.0 equiv.) in anhydrous THF (15 mL) was added dropwise. The resulting mixture stirred for 1 h resulting in a dark red solution. Then the alkyl bromide (23 mmol, 1.0 equiv.) in anhydrous THF (10 mL) was added dropwise at  $-78^\circ\text{C}$ . After stirring for 1 h, the temperature was warmed to room temperature and stirred overnight. The reaction mixture was quenched with saturated  $\text{NH}_4\text{Cl}(\text{aq.})$  (50 mL). The layers were separated and the water layer was extracted with EtOAc (3  $\times$ ). The organic layers were combined, washed with brine, dried with anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude product was purified by flash column chromatography providing the alkylpyridines as slightly yellow liquids.

**General Procedure II: Synthesis of 4-Cycloalkylpyridines (11g and 11h):** A flame dried three-neck round-bottomed flask under  $\text{N}_2$  atmosphere was charged with a solution of diisopropylamine (10.0 mL, 71.3 mmol, 3.1 equiv.) in anhydrous THF (100 mL). The reaction mixture was cooled to  $-78^\circ\text{C}$  and a solution of *n*-butyl-

lithium (2.5 M in THF, 27.6 mL, 69.0 mmol, 3.0 equiv.) was added dropwise. After 10 min, the solution was warmed to  $0^\circ\text{C}$  and stirred for another 20 min. The solution was cooled to  $-78^\circ\text{C}$  and 4-picoline (2.24 mL, 23 mmol, 1.0 equiv.) in anhydrous THF (15 mL) was added dropwise. The resulting mixture was stirred for 1 h resulting in a dark red solution. Then the dibromoalkane (23 mmol, 1 equiv.) in anhydrous THF (10 mL) was added drop wise at  $-78^\circ\text{C}$ . After stirring for 1 h, the temperature was warmed to room temperature and the resulting mixture stirred overnight. The reaction mixture was quenched with saturated  $\text{NH}_4\text{Cl}(\text{aq.})$  (50 mL). The layers were separated and the water layer was extracted with EtOAc (3  $\times$ ). The organic layers were combined, washed with brine, dried with anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude product was purified by flash column chromatography providing the cycloalkylpyridines.

### General Procedure III: Synthesis of 4-Alkylpiperidinium Salts

**(4):** To a three-neck round-bottomed flask charged with 4-(cyclo)-alkylpyridine (11a–h) 10 (12.5 mmol, 1.0 equiv.) were added HCl in methanol (1.25 M, 25.0 mL, 31.3 mmol, 2.5 equiv.) and  $\text{PtO}_2$  (0.14 g, 0.63 mmol, 0.05 equiv.). The flask was evacuated and flushed with  $\text{H}_2$  (3  $\times$ ) using a balloon. The mixture was stirred overnight at room temperature under hydrogen atmosphere. Upon completion, the reaction mixture was filtered through Celite and the residue was washed with additional methanol. The filtrate was concentrated under reduced pressure to afford the title products generally as a white solid.

**Synthesis of 4-Propylpyridine (11b):** Prepared according to general procedure I using bromoethane (1.72 mL, 23 mmol, 1 equiv.). Flash chromatography (cyclohexane/EtOAc = 3:2) provided the product as a yellow liquid (2.69 g, 22.2 mmol, 97 %). RF = 0.37 (cyclohexane/EtOAc = 1:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.39 (d,  $J$  = 5.9 Hz, 2H), 7.01 (d,  $J$  = 5.9 Hz, 2H), 2.49 (t,  $J$  = 7.5 Hz, 2H), 1.56 (tq,  $J$  = 7.5, 7.5 Hz, 2H), 0.86 (t,  $J$  = 7.5 Hz, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  151.3 (Cq), 149.3 (CH), 123.7 (CH), 37.0 ( $\text{CH}_2$ ), 23.2 ( $\text{CH}_2$ ), 13.5 ( $\text{CH}_3$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2960, 2933, 2871, 1600, 1413, 1220, 794, 626, 445; HRMS (ESI):  $m/z$  calculated for  $\text{C}_8\text{H}_{12}\text{N}$  [ $\text{M} + \text{H}$ ] $^+$  122.0964, found 122.0969.

**Synthesis of 4-Butylpyridine (11c):** Prepared according to general procedure I using 1-bromopropane (2.09 mL, 23 mmol, 1 equiv.). Flash chromatography (cyclohexane/EtOAc = 3:1) provided the product as a yellow liquid (3.01 g, 22.3 mmol, 97 %). RF = 0.23 (cyclohexane/EtOAc = 3:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.39 (d,  $J$  = 5.8 Hz, 2H), 7.02 (d,  $J$  = 5.8 Hz, 2H), 2.51 (t,  $J$  = 7.5 Hz, 2H), 1.52 (tt,  $J$  = 7.5, 7.5 Hz, 2H), 1.26 (tq,  $J$  = 7.5, 7.5 Hz, 2H), 0.85 (t,  $J$  = 7.5 Hz, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  151.5 (Cq), 149.4 (CH), 123.7 (CH), 34.7 ( $\text{CH}_2$ ), 32.2 ( $\text{CH}_2$ ), 22.0 ( $\text{CH}_2$ ), 13.6 ( $\text{CH}_3$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2965, 2931, 2860, 1600, 1413, 993, 804, 733, 630, 582, 526, 501; HRMS (ESI):  $m/z$  calculated for  $\text{C}_9\text{H}_{14}\text{N}$  [ $\text{M} + \text{H}$ ] $^+$  136.1121, found 136.1121.

**Synthesis of 4-Isobutylpyridine (11d):** Prepared according to general procedure I using 2-bromopropane (2.16 mL, 23 mmol, 1 equiv.). Flash chromatography (cyclohexane/EtOAc = 5:1) provided the product as a colorless oily liquid (2.67 g, 19.7 mmol, 86 %). RF = 0.40 (cyclohexane/EtOAc = 2:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.37 (d,  $J$  = 5.8 Hz, 2H), 6.94 (d,  $J$  = 5.8 Hz, 2H), 2.33 (d,  $J$  = 7.3 Hz, 2H), 1.77 (tq,  $J$  = 7.3, 7.3, 7.3 Hz, 1H), 0.78 (d,  $J$  = 7.3 Hz, 6H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  150.1 (Cq), 149.2 (CH), 124.2 (CH), 44.3 ( $\text{CH}_2$ ), 29.2 (CH), 22.0 ( $\text{CH}_3$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2965, 2925, 2898, 1602, 1415, 784, 630, 595, 536, 490; HRMS (ESI):  $m/z$  calculated for  $\text{C}_9\text{H}_{14}\text{N}$  [ $\text{M} + \text{H}$ ] $^+$  136.1121, found 136.1122.

**Synthesis of 4-Pentylpyridine (11f):** Prepared according to general procedure I using 1-bromobutane (2.47 mL, 23 mmol, 1 equiv.).

Flash chromatography (cyclohexane/EtOAc = 5:1) provided the product as a yellow liquid (3.07 g, 20.6 mmol, 90 %). RF = 0.45 (cyclohexane/EtOAc = 2:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.49 (bs, 2H), 7.10 (bs, 2H), 2.59 (t,  $J$  = 7.5 Hz, 2H), 1.62 (p,  $J$  = 7.5 Hz, 2H), 1.32 (m, 4H), 0.89 (t,  $J$  = 7.5 Hz, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  151.7 ( $\text{C}_q$ ), 149.6 (CH), 123.9 (CH), 35.2 ( $\text{CH}_2$ ), 31.3 ( $\text{CH}_2$ ), 30.0 ( $\text{CH}_2$ ), 22.4 ( $\text{CH}_2$ ), 14.0 ( $\text{CH}_3$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2965, 2927, 2858, 1600, 1413, 991, 798, 630, 536, 503, 496; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{10}\text{H}_{16}\text{N}$  [ $\text{M} + \text{H}$ ] $^+$  150.1277, found 150.1278.

**Synthesis of 4-Cyclopentylpyridine (11g):** Prepared according to general procedure II using 1,4-dibromobutane (2.75 mL, 23 mmol, 1 equiv.). Flash chromatography (cyclohexane/EtOAc = 3:1) provided the title product as a yellow liquid (0.82 g, 5.57 mmol, 24 %). RF = 0.33 (cyclohexane/EtOAc = 2:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.47 (d,  $J$  = 4.8 Hz, 2H), 7.14 (d,  $J$  = 4.8 Hz, 2H), 2.97 (tt,  $J$  = 8.3, 8.3 Hz, 1H), 2.07 (m, 2H), 1.81 (m, 2H), 1.69 (m, 2H), 1.58 (m, 2H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  155.5 ( $\text{C}_q$ ), 149.6 (CH), 122.6 (CH), 45.1 (CH), 33.9 ( $\text{CH}_2$ ), 25.5 ( $\text{CH}_2$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2948, 2867, 1596, 1409, 993, 813, 630, 545, 493; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{10}\text{H}_{14}\text{N}$  [ $\text{M} + \text{H}$ ] $^+$  148.1121, found 148.1120.

**Synthesis of 4-Cyclohexylpyridine (11h):** Prepared according to general procedure II using 1,4-dibromopentane (3.13 mL, 23 mmol, 1 equiv.). Column chromatography (cyclohexane/EtOAc = 3:1) provided the title product as a yellow liquid (0.91 g, 5.66 mmol, 25 %). RF = 0.34 (cyclohexane/EtOAc = 3:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.47 (d,  $J$  = 4.8 Hz, 2H), 7.11 (d,  $J$  = 4.8 Hz, 2H), 2.48 (m, 1H), 1.85 (m, 4H), 1.75 (d,  $J$  = 12.5 Hz, 1H), 1.40 (m, 4H), 1.25 (m, 1H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  156.5 ( $\text{C}_q$ ), 149.7 (CH), 122.4 (CH), 43.8 (CH), 33.5 ( $\text{CH}_2$ ), 36.50 ( $\text{CH}_2$ ), 25.9 ( $\text{CH}_2$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2923, 2850, 1597, 1448, 1409, 991, 811, 622, 555, 493, 420; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{11}\text{H}_{16}\text{N}$  [ $\text{M} + \text{H}$ ] $^+$  162.1277, found 162.1278.

**Synthesis of 4-Ethylpiperidine Hydrochloride (4a):** Prepared according to general procedure III from commercial 4-ethylpyridine (1.34 g, 12.5 mmol, 1 equiv.). The title compound was isolated as a white solid (1.87 g, 12.5 mmol, 100 %). m.p. 176 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  9.53 (bs, 1H), 9.21 (bs, 1H), 3.45 (m, 2H), 2.83 (m, 2H), 1.88 (d,  $J$  = 13.0 Hz, 2H), 1.59 (m, 2H), 1.46–1.25 (m, 3H), 0.88 (t,  $J$  = 7.0 Hz, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  44.1 ( $\text{CH}_2$ ), 35.8 (CH), 28.4 ( $\text{CH}_2$ ), 28.4 ( $\text{CH}_2$ ), 10.9 ( $\text{CH}_3$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2973, 2794, 2727, 2497, 1593, 1456, 1396, 1076, 993, 574, 441; HRMS (ESI):  $m/z$  calculated for  $\text{C}_7\text{H}_{16}\text{N}$  [ $\text{M} + \text{H}$ ] $^+$  114.1277, found 114.1281.

**Synthesis of 4-Propylpiperidine Hydrochloride (4b):** Prepared according to general procedure III from **11c** (1.51 g, 12.5 mmol, 1 equiv.). The title compound was isolated as an off-white solid (2.04 g, 12.5 mmol, 100 %). m.p. 203 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  9.53 (bs, 1H), 9.22 (bs, 1H), 3.44 (m, 2H), 2.82 (m, 2H), 1.93 (d,  $J$  = 12.5 Hz, 2H), 1.64–1.44 (m, 3H), 1.27 (m, 4H), 0.87 (t,  $J$  = 6.5 Hz, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  44.1 ( $\text{CH}_2$ ), 37.8 ( $\text{CH}_2$ ), 33.8 (CH), 28.7 ( $\text{CH}_2$ ), 19.4 ( $\text{CH}_2$ ), 14.0 ( $\text{CH}_3$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2941, 2923, 2796, 2718, 1591, 1456, 1392, 1074, 956, 574; HRMS (ESI):  $m/z$  calculated for  $\text{C}_8\text{H}_{18}\text{N}$  [ $\text{M} + \text{H}$ ] $^+$  128.1434, found 128.1434.

**Synthesis of 4-Butylpiperidine Hydrochloride (4c):** Prepared according to general procedure III from **11c** (1.69 g, 12.5 mmol, 1 equiv.). The title compound was isolated as an off-white solid (2.22 g, 12.5 mmol, 100 %). m.p. 204 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  9.50 (bs, 1H), 9.21 (bs, 1H), 3.43 (m, 2H), 2.81 (m, 2H), 1.84 (d,  $J$  = 12.5 Hz, 2H), 1.59 (m, 2H), 1.45 (m, 1H), 1.24 (m, 6H), 0.84 (t,  $J$  = 6.3 Hz, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  44.1 ( $\text{CH}_2$ ), 35.3 ( $\text{CH}_2$ ), 34.0 (CH), 28.7 ( $\text{CH}_2$ ), 28.5 ( $\text{CH}_2$ ), 22.6 ( $\text{CH}_2$ ), 13.9 ( $\text{CH}_3$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2947, 2920, 2844, 2792, 2769, 2719, 1591, 1448, 1074, 943, 576, 439; HRMS (ESI):  $m/z$  calculated for  $\text{C}_9\text{H}_{20}\text{N}$  [ $\text{M} + \text{H}$ ] $^+$  142.1590, found 142.1587.

**Synthesis of 4-(Isobutyl)piperidine Hydrochloride (4d):** Prepared according to general procedure III from **11d** (1.69 g, 12.5 mmol, 1 equiv.). The title compound was isolated as a white solid (2.21 g, 12.5 mmol, 100 %). m.p. 259 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  9.57 (bs, 1H), 9.25 (bs, 1H), 3.46 (m, 2H), 2.84 (m, 2H), 1.85 (m, 2H), 1.61 (m, 4H), 1.17 (m, 2H), 0.86 (d,  $J$  = 6.2 Hz, 6H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  44.9 ( $\text{CH}_2$ ), 44.1 ( $\text{CH}_2$ ), 31.7 (CH), 28.9 ( $\text{CH}_2$ ), 24.4 (CH), 22.6 ( $\text{CH}_3$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2890, 2796, 2769, 2736, 1589, 1448, 595, 499; HRMS (ESI):  $m/z$  calculated for  $\text{C}_9\text{H}_{20}\text{N}$  [ $\text{M} + \text{H}$ ] $^+$  142.1590, found 142.1587.

**Synthesis of 4-(tert-Butyl)piperidine Hydrochloride (4e):** Prepared according to general procedure III from commercial 4-tert-butylpyridine (1.69 g, 12.5 mmol, 1 equiv.) with additional  $\text{PtO}_2$  (0.10 equiv. instead of 0.05 equiv.) and a prolonged reaction time (36 h instead of overnight). The title compound was isolated as a white solid (2.07 g, 12.5 mmol, 93 %). m.p. 303 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  9.54 (bs, 1H), 9.23 (bs, 1H), 3.53 (d,  $J$  = 12.0 Hz, 2H), 2.79 (q,  $J$  = 12.0 Hz, 2H), 1.85 (d,  $J$  = 12.0 Hz, 2H), 1.70 (q,  $J$  = 12.0 Hz, 2H), 1.21 (t,  $J$  = 12.0 Hz, 1H), 0.87 (s, 9H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  44.8 (CH), 44.7 ( $\text{CH}_2$ ), 32.3 ( $\text{C}_q$ ), 27.0 ( $\text{CH}_3$ ), 23.9 ( $\text{CH}_2$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2960, 2837, 2798, 2777, 2761, 2744, 2719, 1591, 1448, 1396, 1361, 1078, 568, 509; HRMS (ESI):  $m/z$  calculated for  $\text{C}_9\text{H}_{20}\text{N}$  [ $\text{M} + \text{H}$ ] $^+$  142.1590, found 142.1588.

**Synthesis of 4-Pentylpiperidine Hydrochloride (4f):** Prepared according to general procedure III from **11f** (1.87 g, 12.5 mmol, 1 equiv.). The title compound was isolated as an off-white solid (2.39 g, 12.5 mmol, 100 %). m.p. 201 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  9.55 (bs, 1H), 9.23 (bs, 1H), 3.45 (m, 2H), 2.81 (m, 2H), 1.87 (d,  $J$  = 12.5 Hz, 2H), 1.60 (m, 2H), 1.47 (m, 1H), 1.26 (m, 8H), 0.86 (t,  $J$  = 6.5 Hz, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  44.1 ( $\text{CH}_2$ ), 35.6 ( $\text{CH}_2$ ), 34.1 (CH), 31.8 ( $\text{CH}_2$ ), 28.8 ( $\text{CH}_2$ ), 26.0 ( $\text{CH}_2$ ), 22.5 ( $\text{CH}_2$ ), 14.0 ( $\text{CH}_3$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2945, 2910, 2846, 2792, 2767, 2734, 1589, 1448, 1396, 1074, 576, 437; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{10}\text{H}_{22}\text{N}$  [ $\text{M} + \text{H}$ ] $^+$  156.1747, found 156.1746.

**Synthesis of 4-Cyclopentylpiperidine Hydrochloride (4g):** Prepared according to general procedure III from **11g** (0.72 g, 4.89 mmol, 1 equiv.) on a smaller scale. The title compound was isolated as an off-white solid (0.92 g, 4.85 mmol, 99 %). m.p. 238 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  9.45 (bs, 1H), 9.16 (bs, 1H), 3.45 (m, 2H), 2.81 (m, 2H), 1.98–1.43 (m, 9H), 1.24 (m, 1H), 1.05 (m, 2H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  45.1 (CH), 44.3 ( $\text{CH}_2$ ), 39.9 (CH), 30.2 ( $\text{CH}_2$ ), 27.9 ( $\text{CH}_2$ ), 25.0 ( $\text{CH}_2$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2966, 2850, 2792, 2765, 2738, 2704, 2495, 1589, 1444, 1396, 1076, 522; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{10}\text{H}_{20}\text{N}$  [ $\text{M} + \text{H}$ ] $^+$  154.1590, found 154.1588.

**Synthesis of 4-Cyclohexylpiperidine Hydrochloride (4h):** Prepared according to general procedure III from **11h** (0.68 g, 4.22 mmol, 1 equiv.) on a smaller scale. The title compound was isolated as an off-white solid (0.79 g, 3.88 mmol, 92 %). m.p. 310 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  9.51 (bs, 1H), 9.19 (bs, 1H), 3.48 (d,  $J$  = 12.0 Hz, 2H), 2.79 (m, 2H), 1.91–1.60 (m, 9H), 1.32–1.02 (m, 5H), 0.91 (q,  $J$  = 12.0 Hz, 2H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  44.4 ( $\text{CH}_2$ ), 41.8 (CH), 39.8 (CH), 29.9 ( $\text{CH}_2$ ), 26.4 ( $\text{CH}_2$ ), 26.3 ( $\text{CH}_2$ ), 26.1 ( $\text{CH}_2$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2964, 2848, 2794, 2777, 2727, 1450, 541; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{11}\text{H}_{22}\text{N}$  [ $\text{M} + \text{H}$ ] $^+$  168.1747, found 168.1745.

#### Synthesis of the Pipecolic Amides (6)

**General Procedure IV: 3-Step Synthesis of the U-3CR Products:** The 4-alkyl piperidinium salt **4** (6.0 mmol, 1 equiv.) was dissolved in water and the pH was increased to >11 by addition of aqueous  $\text{NH}_4\text{OH}$  (25 % w/w). The resulting solution was extracted  $\text{CH}_2\text{Cl}_2$



(2 ×). The organic layers were combined, washed with brine, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The remaining oil was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and the solution was cooled to 0 °C. Then, *N*-chlorosuccinimide (0.82 g, 6.12 mmol, 1.02 equiv.) was added portion-wise (over 5 min) to the solution. The ice bath was removed and the resulting mixture was stirred for 3 h until TLC indicated a clear sign of the chlorinated species (clearly visible under UV at relatively high R<sub>F</sub> values). Upon completion, the reaction mixture was washed with water (2 ×) and with brine, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The remaining oil was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and slowly added to a solution of KOH (0.71 g, 12.6 mmol, 2.1 equiv.) in EtOH (15 mL) and the resulting mixture was stirred overnight. Upon completion, the mixture was filtered and the filtrate was concentrated under reduced pressure. The remaining mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, washed with water (2 ×) and with brine, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under reduced pressure to afford the corresponding imine **5**. Batches of 1.0 mmol of crude imine were used in the U-3CR reaction without further purification. Thus, in a round-bottom flask, **5** (1 mmol, 1 equiv.) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). Then, the isocyanide **13** (1.2 mmol, 1.2 equiv.) and the carboxylic acid **14** (1.2 mmol, 1.2 equiv.) were added sequentially and the resulting mixture was stirred for 48 h. More CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added and the resulting solution was washed with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> and with brine, dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography to obtain the product generally as a white solid.

**Synthesis of *N*-Cyclohexyl-4-ethyl-1-pivaloylpiperidine-2-carboxamide (6a):** The general procedure IV with 0.90 g (6.0 mmol, 1 equiv.) of **4a** gave 0.54 g (4.86 mmol, 81 %) of 3,4,5,6-tetrahydro-4-ethylpyridine **5b**. An 1.0 mmol aliquot of **5b** (111 mg, 1 equiv.) was then used in the U-3CR together with pivalic acid (123 mg, 1.2 mmol, 1.2 equiv.) and cyclohexyl isocyanide (149 µL, 1.2 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (cyclohexane/EtOAc = 6:1) provided the **6a** as a white solid (254 mg, 0.79 mmol, 79 %). RF = 0.66 (cyclohexane/EtOAc = 2:1); m.p. 107–108 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 6.08 (bs, 1H), 5.09 (m, 1H), 4.16 (m, 1H), 3.72 (q, *J* = 4.3 Hz, 1H), 2.88 (m, 1H), 2.28 (d, *J* = 12.8 Hz, 1H), 1.87–1.51 (m, 7H), 1.34–0.95 (m, 19H), 0.87 (t, *J* = 7.0 Hz, 3H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): δ 178.2 (C<sub>q</sub>), 170.0 (C<sub>q</sub>), 47.6 (CH), 44.0 (C<sub>q</sub>), 38.8 (CH<sub>2</sub>), 33.4 (CH), 33.1 (CH<sub>2</sub>), 32.7 (CH<sub>2</sub>), 31.7 (CH<sub>2</sub>), 31.4 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 28.2 (CH<sub>3</sub>), 25.4 (CH<sub>2</sub>), 24.5 (CH<sub>2</sub>), 10.9 (CH<sub>3</sub>) ppm; IR (neat):  $\tilde{\nu}_{\max}$  (cm<sup>-1</sup>) = 3325, 2928, 2854, 1670, 1610, 1522, 1412, 1188, 919, 729, 646; HRMS (ESI): *m/z* calculated for C<sub>19</sub>H<sub>34</sub>N<sub>2</sub>NaO<sub>2</sub> [M + Na]<sup>+</sup> 345.2512, found 345.2512.

**Synthesis of *N*-(*tert*-Butyl)-4-ethyl-1-(2-(4-methoxyphenyl)-acetyl)-piperidine-2-carboxamide (6b):** Another 1.0 mmol aliquot of **5b** (111 mg, 1 equiv., see preparation of **6a**) was then used in the U-3CR together with 4-methoxyphenylacetic acid (199 mg, 1.2 mmol, 1.2 equiv.) and *tert*-butyl isocyanide (135 µL, 1.2 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (cyclohexane/EtOAc = 4:1) provided **6b** as an off-white solid (292 mg, 0.81 mmol, 81 %). Two rotamers were present on NMR-timescale in a 1:0.28 ratio. RF = 0.41 (cyclohexane/EtOAc = 2:1); m.p. 90 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 7.16 (m, 2.56H), 6.83 (d, *J* = 8.6 Hz, 2.56H), 5.9 (bs, 1H), 5.25 (bs, 0.28H), 5.15 (d, *J* = 5.5 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 0.28H), 4.44 (d, *J* = 5.0 Hz, 0.28H), 3.89–3.61 (m, 7.40H), 2.90 (t, *J* = 11.4 Hz, 1H), 2.43 (m, 0.56H), 2.21 (d, *J* = 12.0 Hz, 1H), 1.78–1.60 (m, 2.28H), 1.30–1.08 (m, 14.36H), 1.05–0.79 (m, 6.40H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): δ 171.3 (C<sub>q</sub>), 171.1 (C<sub>q</sub>), 169.9 (C<sub>q</sub>), 168.1 (C<sub>q</sub>), 158.6 (C<sub>q</sub>), 158.5 (C<sub>q</sub>), 129.4 (CH), 129.3 (CH),

126.6 (C<sub>q</sub>), 126.4 (C<sub>q</sub>), 114.5 (CH), 114.2 (CH), 58.3 (CH), 55.2 (CH), 55.2 (CH<sub>3</sub>), 52.4 (CH<sub>3</sub>), 51.0 (C<sub>q</sub>), 50.8 (C<sub>q</sub>), 44.1 (CH<sub>2</sub>), 40.7 (CH<sub>2</sub>), 40.1 (CH<sub>2</sub>), 39.9 (CH<sub>2</sub>), 33.7 (CH), 33.0 (CH), 32.4 (CH<sub>2</sub>), 31.4 (CH<sub>2</sub>), 31.2 (CH<sub>2</sub>), 30.7 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 29.1 (CH<sub>2</sub>), 28.6 (CH<sub>3</sub>), 28.3 (CH<sub>3</sub>), 10.8 (CH<sub>3</sub>), 10.7 (CH<sub>3</sub>); IR (neat):  $\tilde{\nu}_{\max}$  (cm<sup>-1</sup>) = 3325, 2959, 1624, 1510, 1452, 1246, 1036, 920, 731, 644, 523; HRMS (ESI): *m/z* calculated for C<sub>21</sub>H<sub>33</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup> 361.2486, found 361.2465.

**Synthesis of *N*-Pentyl-1-pivaloyl-4-propylpiperidine-2-carboxamide (6c):** The general procedure IV with 0.98 g (6.0 mmol, 1 equiv.) of **4b** gave 0.64 g (5.1 mmol, 85 %) of 3,4,5,6-tetrahydro-4-propylpyridine **5c**. An 1.0 mmol aliquot of **5c** (125 mg, 1 equiv.) was then used in the U-3CR together with pivalic acid (123 mg, 1.2 mmol, 1.2 equiv.) and cyclohexyl isocyanide (151 µL, 1.2 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (cyclohexane/EtOAc = 5:1) provided **6c** as a slowly crystallizing oil (254 mg, 0.78 mmol, 78 %). RF = 0.58 (cyclohexane/EtOAc = 2:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 6.21 (bs, 1H), 5.10 (bs, 1H), 4.15 (m, 1H), 3.26 (m, 1H), 3.11 (m, 1H), 2.92 (m, 1H), 2.27 (d, *J* = 12.9 Hz, 1H), 1.85 (m, 1H), 1.67 (d, *J* = 12.9 Hz, 1H), 1.42 (m, 2H), 1.33–1.10 (m, 17H), 1.10–0.99 (m, 2H), 0.86 (m, 6H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): δ 178.3 (C<sub>q</sub>), 171.0 (C<sub>q</sub>), 45.3 (CH), 44.2 (C<sub>q</sub>), 39.1 (CH<sub>2</sub>), 38.9 (CH<sub>2</sub>), 38.9 (CH<sub>2</sub>), 32.0 (CH<sub>2</sub>), 31.8 (CH<sub>2</sub>), 31.4 (CH), 29.3 (CH<sub>2</sub>), 29.0 (CH<sub>2</sub>), 28.2 (CH<sub>3</sub>), 22.2 (CH<sub>2</sub>), 19.5 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>), 13.9 (CH<sub>3</sub>) ppm; IR (neat):  $\tilde{\nu}_{\max}$  (cm<sup>-1</sup>) = 3337, 2955, 2928, 1670, 1612, 1521, 1412, 1186, 630, 532; HRMS (ESI): *m/z* calculated for C<sub>19</sub>H<sub>36</sub>N<sub>2</sub>NaO<sub>2</sub> [M + Na]<sup>+</sup> 347.2669, found 347.2670.

**Synthesis of 1-Benzoyl-*N*-(*tert*-butyl)-4-propylpiperidine-2-carboxamide (6d):** Another 1.0 mmol aliquot of **5c** (125 mg, 1 equiv., see preparation of **6c**) was then used in the U-3CR together with benzoic acid (147 mg, 1.2 mmol, 1.2 equiv.) and *tert*-butyl isocyanide (135 µL, 1.2 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (cyclohexane/EtOAc = 4:1) provided **6d** as a slowly crystallizing white solid (271 mg, 0.82 mmol, 82 %). Two rotamers were present on NMR-timescale in a 1:0.21 ratio. RF = 0.57 (cyclohexane/EtOAc = 2:1); m.p. 92 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 7.44–7.26 (m, 6.05H), 6.41 (s, 1H), 5.81 (s, 0.21H), 5.17 (d, *J* = 5.4 Hz, 1H), 4.72 (d, *J* = 12.8 Hz, 0.21H), 4.29 (bs, 0.21H), 3.76 (d, *J* = 13.6 Hz, 1H), 3.01 (t, *J* = 11.6 Hz, 1H), 2.79 (t, *J* = 12.6 Hz, 0.21H), 2.78 (d, *J* = 13.2 Hz, 1.21H), 1.96 (m, 1H), 1.75 (d, *J* = 12.7 Hz, 0.21H), 1.62 (d, *J* = 12.8 Hz, 1H), 1.50 (m, 0.42H), 1.40–1.02 (m, 18.15H), 0.87 (m, 3.63H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): δ 172.0 (C<sub>q</sub>), 171.8 (C<sub>q</sub>), 170.0 (C<sub>q</sub>), 168.8 (C<sub>q</sub>), 135.5 (C<sub>q</sub>), 135.3 (C<sub>q</sub>), 130.1 (CH), 129.9 (CH), 128.7 (CH), 128.5 (CH), 126.9 (CH), 126.1 (CH), 59.7 (CH), 53.2 (CH), 51.5 (C<sub>q</sub>), 50.9 (C<sub>q</sub>), 45.8 (CH<sub>2</sub>), 40.2 (CH<sub>2</sub>), 39.0 (CH<sub>2</sub>), 38.6 (CH<sub>2</sub>), 33.4 (CH<sub>2</sub>), 33.1 (CH<sub>2</sub>), 32.1 (CH<sub>2</sub>), 31.8 (CH), 31.4 (CH), 31.3 (CH<sub>2</sub>), 28.8 (CH<sub>3</sub>), 28.7 (CH<sub>3</sub>), 19.5 (CH<sub>2</sub>), 19.4 (CH<sub>2</sub>), 14.3 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>) ppm; IR (neat):  $\tilde{\nu}_{\max}$  (cm<sup>-1</sup>) = 3337, 2959, 2926, 1683, 1616, 1522, 1423, 1363, 1253, 1224, 1203, 921, 730, 700, 646; HRMS (ESI): *m/z* calculated for C<sub>20</sub>H<sub>31</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup> 331.2380, found 331.2367.

**Synthesis of Methyl (1-Acetyl-4-butylpiperidine-2-carbonyl)-glycinate (6e):** The general procedure IV with 1.07 g (6.0 mmol, 1 equiv.) of **4c** gave 0.78 g (5.6 mmol, 93 %) of 3,4,5,6-tetrahydro-4-butylpyridine **5d**. An 1.0 mmol aliquot of **5d** (139 mg, 1 equiv.) was then used in the U-3CR together with acetic acid (69 µL, 1.2 mmol, 1.2 equiv.) and methyl isocyanoacetate (109 µL, 1.2 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (EtOAc) provided **6e** as a slowly crystallizing oil (205 mg, 0.69 mmol, 69 %). Two rotamers were present on NMR-timescale in a 1:0.27 ratio. RF = 0.25 (EtOAc); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 7.27 (bs, 0.27H), 6.69 (bs, 1H), 5.28 (d, *J* = 5.5 Hz, 1H), 4.59 (d, *J* = 13.5 Hz, 0.27H), 4.46 (d, *J* = 5.2 Hz, 0.27H), 4.14 (m, 1.27H), (dd, *J* = 17.8,

5.5 Hz, 0.27H), 3.80–3.70 (m, 5.81H), 3.21 (dt,  $J = 13.8, 2.2$  Hz, 1H), 2.71 (dt,  $J = 13.3, 2.5$  Hz, 0.27H), 2.52 (d,  $J = 12.4$  Hz, 0.27H), 2.26 (d,  $J = 12.2$  Hz, 1H), 2.16 (s, 3H), 2.11 (s, 0.81H), 1.93 (bs, 0.27H), 1.80–1.63 (m, 2.27H), 1.43 (bs, 0.27H), 1.80–1.63 (m, 9.89H), 0.86 (t,  $J = 6.8$  Hz, 3.81H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  171.4 ( $\text{C}_q$ ), 170.9 ( $\text{C}_q$ ), 170.4 ( $\text{C}_q$ ), 170.4 ( $\text{C}_q$ ), 170.3 ( $\text{C}_q$ ), 170.2 ( $\text{C}_q$ ), 58.2 (CH), 52.3 (CH), 52.2 ( $\text{CH}_2$ ), 51.8 ( $\text{CH}_2$ ), 44.4 ( $\text{CH}_2$ ), 41.0 ( $\text{CH}_2$ ), 40.8 ( $\text{CH}_2$ ), 39.5 ( $\text{CH}_2$ ), 36.3 ( $\text{CH}_2$ ), 36.1 ( $\text{CH}_2$ ), 33.0 ( $\text{CH}_2$ ), 32.1 (CH), 31.9 ( $\text{CH}_2$ ), 31.7 ( $\text{CH}_2$ ), 31.5 (CH), 31.2 ( $\text{CH}_2$ ), 29.7 ( $\text{CH}_2$ ), 28.5 ( $\text{CH}_2$ ), 28.5 ( $\text{CH}_2$ ), 22.7 ( $\text{CH}_2$ ), 21.7 ( $\text{CH}_3$ ), 21.7 ( $\text{CH}_3$ ), 14.0 ( $\text{CH}_3$ ), 14.0 ( $\text{CH}_3$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3330, 2925, 1751, 1629, 1521, 1423, 1363, 1201, 644, 572, 463; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{15}\text{H}_{27}\text{N}_2\text{O}_4$  [ $\text{M} + \text{H}$ ] $^+$  299.1965, found 299.1949.

**Synthesis of *N*-(*tert*-Butyl)-4-butyl-1-(pent-4-enoyl)piperidine-2-carboxamide (6f):** Another 1.0 mmol aliquot of **5d** (139 mg, 1 equiv.) was then used in the U-3CR together with 4-pentenoic acid (123  $\mu\text{L}$ , 1.2 mmol, 1.2 equiv.) and *tert*-butyl isocyanide (135  $\mu\text{L}$ , 1.2 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (cyclohexane/EtOAc = 4:1) provided **6f** as a white solid (270 mg, 0.84 mmol, 84 %). Two rotamers were present on NMR-timescale in a 1:0.25 ratio. RF = 0.58 (cyclohexane/EtOAc = 2:1) m.p. 89 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  5.97 (s, 1H), 5.84 (m, 1.25H), 5.70 (s, 0.25H), 5.11 (d,  $J = 6.5$  Hz, 1H), 5.05 (d,  $J = 17.2$  Hz, 1.25H), 4.99 (d,  $J = 10.2$  Hz, 1.25H), 4.63 (d,  $J = 11.7$  Hz, 0.25H), 4.38 (d,  $J = 5.4$  Hz, 0.25H), 3.76 (d,  $J = 13.6$  Hz, 1H), 3.05 (dt,  $J = 13.3, 2.5$  Hz, 1H), 2.55–2.31 (m, 5.5H), 2.18 (d,  $J = 13.5$  Hz, 1H), 1.83 (m, 1H), 1.70 (m, 1.25H), 1.31–1.12 (m, 19.0H) 1.08–0.95 (m, 2.5H), 0.85 (t,  $J = 7.0$  Hz, 3.75H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  172.4 ( $\text{C}_q$ ), 172.0 ( $\text{C}_q$ ), 170.2 ( $\text{C}_q$ ), 168.7 ( $\text{C}_q$ ), 137.1 ( $\text{CH}_2$ ), 137.0 ( $\text{CH}_2$ ), 115.6 (CH), 115.4 (CH), 57.7 (CH), 52.5 (CH), 51.5 ( $\text{C}_q$ ), 50.8 ( $\text{C}_q$ ), 43.5 ( $\text{CH}_2$ ), 39.7 ( $\text{CH}_2$ ), 36.4 ( $\text{CH}_2$ ), 36.1 ( $\text{CH}_2$ ), 33.0 ( $\text{CH}_2$ ), 32.7 ( $\text{CH}_2$ ), 32.6 ( $\text{CH}_2$ ), 32.3 (CH), 32.1 ( $\text{CH}_2$ ), 31.8 ( $\text{CH}_2$ ), 31.6 (CH), 31.2 ( $\text{CH}_2$ ), 29.2 ( $\text{CH}_2$ ), 29.2 ( $\text{CH}_2$ ), 28.7 ( $\text{CH}_3$ ), 28.7 ( $\text{CH}_3$ ), 28.6 ( $\text{CH}_2$ ), 28.5 ( $\text{CH}_2$ ), 22.8 ( $\text{CH}_2$ ), 22.8 ( $\text{CH}_2$ ), 14.0 ( $\text{CH}_3$ ), 14.0 ( $\text{CH}_3$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3329, 2924, 1676, 1628, 1541, 1452, 1425, 1363, 910, 731, 646; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{19}\text{H}_{34}\text{N}_2\text{NaO}_2$  [ $\text{M} + \text{Na}$ ] $^+$  345.2512, found 345.2528.

**Synthesis of *N*-Cyclohexyl-4-isobutyl-1-pivaloylpiperidine-2-carbox-amide (6g):** The general procedure IV with 1.07 g (6.0 mmol, 1 equiv.) of **4d** gave 0.75 g (5.4 mmol, 90 %) of 3,4,5,6-tetrahydro-4-isobutylpyridine **5e**. An 1.0 mmol aliquot of **5e** (139 mg, 1 equiv.) was then used in the U-3CR together with pivalic acid (123 mg, 1.2 mmol, 1.2 equiv.) and cyclohexyl isocyanide (149  $\mu\text{L}$ , 1.2 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (cyclohexane/EtOAc = 6:1) provided **6g** as a white crystalline solid (286 mg, 0.81 mmol, 81 %). RF = 0.64 (cyclohexane/EtOAc = 2:1); m.p. 96 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  6.13 (bs, 1H), 5.10 (bs, 1H), 4.16 (bs, 1H), 3.74 (m, 1H), 2.91 (m, 1H), 2.27 (d,  $J = 11.8$  Hz, 1H), 1.95 (bs, 1H), 1.84 (d,  $J = 9.2$  Hz, 1H), 1.76 (d,  $J = 9.1$  Hz, 1H), 1.72–1.59 (m, 4H), 2.27 (d,  $J = 9.1$  Hz, 1H), 1.40–1.24 (m, 1H), 1.20–0.96 (m, 7H), 0.89 (d,  $J = 6.6$  Hz, 3H), 0.85 (d,  $J = 6.6$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  178.3 ( $\text{C}_q$ ), 170.1 ( $\text{C}_q$ ), 47.6 (CH), 46.1 ( $\text{CH}_2$ ), 44.2 (CH), 38.8 ( $\text{C}_q$ ), 33.2 ( $\text{CH}_2$ ), 32.8 ( $\text{CH}_2$ ), 32.3 ( $\text{CH}_2$ ), 31.9 ( $\text{CH}_2$ ), 29.4 (CH), 28.2 ( $\text{CH}_3$ ), 25.4 ( $\text{CH}_2$ ), 24.6 ( $\text{CH}_2$ ), 24.5 (CH), 22.9 ( $\text{CH}_3$ ), 22.5 ( $\text{CH}_3$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3339, 2930, 2853, 1678, 1610, 1518, 1412, 1366, 1186, 976, 920, 731, 646, 467; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{21}\text{H}_{38}\text{N}_2\text{NaO}_2$  [ $\text{M} + \text{Na}$ ] $^+$  373.2825, found 373.2833.

**Synthesis of 1-Benzoyl-*N*-(*tert*-butyl)-4-isobutylpiperidine-2-carbox-amide (6h):** Another 1.0 mmol aliquot of **5e** (139 mg, 1 equiv., see preparation of **6g**) was then used in the U-3CR together with benzoic acid (147 mg, 1.2 mmol, 1.2 equiv.) and *tert*-

butyl isocyanide (135  $\mu\text{L}$ , 1.2 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (cyclohexane/EtOAc = 7:2) provided **6h** as a white solid (294 mg, 0.91 mmol, 91 %). Two rotamers were present on NMR-timescale in a 1:0.23 ratio. RF = 0.57 (cyclohexane/EtOAc = 2:1); m.p. 115 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.45–7.35 (m, 6.15H), 6.39 (bs, 1H), 5.78 (bs, 0.23H), 5.18 (d,  $J = 5.4$  Hz, 1H), 4.73 (d,  $J = 12.6$  Hz, 0.23H), 4.30 (bs, 0.23H), 3.67 (d,  $J = 13.7$  Hz, 1H), 3.01 (t,  $J = 12.1$  Hz, 1H), 2.82 (t,  $J = 12.1$  Hz, 0.23H), 2.28 (d,  $J = 13.3$  Hz, 1.23H), 2.03 (m, 1H), 1.76–1.64 (m, 1.69H), 1.61 (d,  $J = 12.8$  Hz, 1.23H), 1.35 (s, 11.07H), 1.19–1.01 (m, 4.92H), 0.91 (d,  $J = 6.6$  Hz, 3.69H), 0.88 (d,  $J = 6.6$  Hz, 3.69H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  172.0 ( $\text{C}_q$ ), 171.9 ( $\text{C}_q$ ), 170.0 ( $\text{C}_q$ ), 168.8 ( $\text{C}_q$ ), 135.5 ( $\text{C}_q$ ), 135.3 ( $\text{C}_q$ ), 130.1 (CH), 130.0 (CH), 128.8 (CH), 128.6 (CH), 127.0 (CH), 126.1 (CH), 59.7 (CH), 53.3 (CH), 51.6 ( $\text{C}_q$ ), 50.9 ( $\text{C}_q$ ), 46.3 ( $\text{CH}_2$ ), 45.8 ( $\text{CH}_2$ ), 45.8 ( $\text{CH}_2$ ), 40.3 ( $\text{CH}_2$ ), 33.2 ( $\text{CH}_2$ ), 32.5 ( $\text{CH}_2$ ), 31.9 ( $\text{CH}_2$ ), 31.7 ( $\text{CH}_2$ ), 30.0 (CH), 29.4 (CH), 28.8 ( $\text{CH}_3$ ), 28.7 ( $\text{CH}_3$ ), 24.6 (CH), 24.5 (CH), 22.9 ( $\text{CH}_3$ ), 22.8 ( $\text{CH}_3$ ), 22.7 ( $\text{CH}_3$ ), 22.6 ( $\text{CH}_3$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3327, 2957, 1682, 1620, 1533, 1425, 1366, 1254, 700; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{21}\text{H}_{33}\text{N}_2\text{O}_2$  [ $\text{M} + \text{H}$ ] $^+$  345.2537, found 345.2529.

**Synthesis of 1-Acetyl-4-(*tert*-butyl)-*N*-pentylpiperidine-2-carbox-amide (6i):** The general procedure IV with 1.07 g (6.0 mmol, 1 equiv.) of **4e** gave 0.71 g (5.1 mmol, 85 %) of 3,4,5,6-tetrahydro-4-*tert*-butylpyridine **5f**. An 1.0 mmol aliquot of **5f** (139 mg, 1 equiv.) was then used in the U-3CR together with acetic acid (69  $\mu\text{L}$ , 1.2 mmol, 1.2 equiv.) and pentyl isocyanide (151  $\mu\text{L}$ , 1.2 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (cyclohexane/EtOAc = 6:1) provided **6i** as a white solid (284 mg, 0.96 mmol, 96 %). Two rotamers were present on NMR-timescale in a 1:0.30 ratio. RF = 0.31 (cyclohexane/EtOAc = 6:1); m.p. 100 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  6.48 (bs, 0.30H), 6.21 (bs, 1H), 5.21 (d,  $J = 4.6$  Hz, 1H), 4.62 (d,  $J = 13.6$  Hz, 0.30H), 4.44 (bs, 0.30H), 3.74 (d,  $J = 12.9$  Hz, 1H), 3.26–3.08 (m, 3.60H), 2.52 (m, 0.60H), 2.22 (d,  $J = 13.1$  Hz, 1H), 2.13 (s, 3H), 2.07 (s, 0.90H), 1.72–1.51 (m, 2.30H), 1.49–1.39 (m, 2.60H), 1.33–1.05 (m, 8.10H), 0.83 (m, 15.60H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  170.8 ( $\text{C}_q$ ), 170.5 ( $\text{C}_q$ ), 170.2 ( $\text{C}_q$ ), 169.3 ( $\text{C}_q$ ), 58.5 (CH), 52.1 (CH), 44.7 ( $\text{CH}_2$ ), 42.3 (CH), 41.4 (CH), 39.9 ( $\text{CH}_2$ ), 32.0 ( $\text{C}_q$ ), 32.0 ( $\text{C}_q$ ), 29.2 ( $\text{CH}_2$ ), 29.0 ( $\text{CH}_2$ ), 29.0 ( $\text{CH}_2$ ), 27.8 ( $\text{CH}_2$ ), 26.9 ( $\text{CH}_3$ ), 26.9 ( $\text{CH}_3$ ), 26.6 ( $\text{CH}_2$ ), 26.6 ( $\text{CH}_2$ ), 25.9 ( $\text{CH}_2$ ), 22.2 ( $\text{CH}_2$ ), 22.2 ( $\text{CH}_2$ ), 21.7 ( $\text{CH}_3$ ), 21.6 ( $\text{CH}_3$ ), 13.9 ( $\text{CH}_3$ ), 13.9 ( $\text{CH}_3$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3319, 2955, 2868, 1631, 1529, 1423, 1365, 1259, 1186, 993, 730, 629, 528; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{17}\text{H}_{32}\text{N}_2\text{NaO}_2$  [ $\text{M} + \text{Na}$ ] $^+$  319.2356, found 319.2369.

**Synthesis of *N*,4-Di-*tert*-butyl-1-(pent-4-enoyl)piperidine-2-carbox-amide (6j):** Another 1.0 mmol aliquot of **5f** (139 mg, 1 equiv., see preparation of **6i**) was then used in the U-3CR together with 4-pentenoic acid (123  $\mu\text{L}$ , 1.2 mmol, 1.2 equiv.) and *tert*-butyl isocyanide (135  $\mu\text{L}$ , 1.2 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (cyclohexane/EtOAc = 4:1) provided **6j** as a white solid (312 mg, 0.97 mmol, 97 %). Two rotamers were present on NMR-timescale in a 1:0.20 ratio. RF = 0.54 (cyclohexane/EtOAc = 2:1); m.p. 126 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  5.96 (bs, 1H), 5.85 (m, 1.20H), 5.69 (bs, 0.20H), 5.16 (d,  $J = 5.7$  Hz, 1H), 5.06 (d,  $J = 17.2$  Hz, 1.20H), 5.00 (d,  $J = 10.2$  Hz, 1.20H), 4.67 (d,  $J = 13.5$  Hz, 0.20H), 4.43 (bs, 0.20H), 3.81 (d,  $J = 13.5$  Hz, 1H), 3.05 (dt,  $J = 13.2, 2.5$  Hz, 1H), 2.53–2.33 (m, 5.20H), 2.19 (d,  $J = 13.3$  Hz, 1H), 1.70 (d,  $J = 12.9$  Hz, 1H), 1.63 (m, 1.20H), 1.33 (s, 1.80H), 1.28 (s, 9H), 1.17 (m, 2.60H), 0.85 (s, 9H), 0.84 (s, 1.80H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  172.3 ( $\text{C}_q$ ), 171.9 ( $\text{C}_q$ ), 170.3 ( $\text{C}_q$ ), 168.7 ( $\text{C}_q$ ), 137.1 (CH), 137.0 (CH), 115.6 ( $\text{CH}_2$ ), 115.4 ( $\text{CH}_2$ ), 57.9 (CH), 52.6 (CH), 51.1 ( $\text{C}_q$ ), 50.8 ( $\text{C}_q$ ), 43.9 ( $\text{CH}_2$ ), 42.4 (CH), 41.3 (CH), 40.2 ( $\text{CH}_2$ ), 32.6 ( $\text{CH}_2$ ), 32.5

(CH<sub>2</sub>), 32.0 (C<sub>q</sub>), 32.0 (C<sub>q</sub>), 29.2 (CH<sub>2</sub>), 29.2 (CH<sub>2</sub>), 28.7 (CH<sub>3</sub>), 28.7 (CH<sub>3</sub>), 27.8 (CH<sub>2</sub>), 27.0 (CH<sub>3</sub>), 26.9 (CH<sub>3</sub>), 26.8 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>) ppm; IR (neat):  $\tilde{\nu}_{\max}$  (cm<sup>-1</sup>) = 3323, 2959, 1682, 1626, 1541, 1450, 1363, 1263, 1224, 910, 632, 530; HRMS (ESI):  $m/z$  calculated for C<sub>19</sub>H<sub>35</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup> 323.2693, found 323.2676.

**Synthesis of *N*-Cyclohexyl-4-pentyl-1-pivaloylpiperidine-2-carbox-amide (6k):** The general procedure IV with 1.15 g (6.0 mmol, 1 equiv.) of **4f** gave 0.85 g (5.5 mmol, 92 %) of 3,4,5,6-tetrahydro-4-pentylpyridine **5g**. An 1.0 mmol aliquot of **5g** (153 mg, 1 equiv.) was then used in the U-3CR together with pivalic acid (123 mg, 1.2 mmol, 1.2 equiv.) and cyclohexyl isocyanide (149  $\mu$ L, 1.2 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (cyclohexane/EtOAc = 6:1) provided **6k** as a white solid (339 mg, 0.93 mmol, 93 %). RF = 0.44. (cyclohexane/EtOAc = 4:1); m.p. 78 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  6.09 (d,  $J$  = 7.4 Hz, 1H), 5.06 (bs, 1H), 4.16 (m, 1H), 3.73 (m, 1H), 2.89 (m, 1H), 2.28 (d,  $J$  = 12.7 Hz, 1H), 1.90–1.72 (m, 3H), 1.71–1.51 (m, 4H), 1.40–0.95 (m, 24H), 0.85 (t,  $J$  = 6.7 Hz, 3H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz):  $\delta$  178.2 (C<sub>q</sub>), 170.0 (C<sub>q</sub>), 47.6 (CH), 44.1 (CH), 38.8 (C<sub>q</sub>), 36.7 (CH<sub>2</sub>), 33.1 (CH<sub>2</sub>), 32.7 (CH<sub>2</sub>), 32.0 (CH<sub>2</sub>), 31.9 (CH<sub>2</sub>), 31.7 (CH), 28.2 (CH<sub>3</sub>), 26.0 (CH<sub>2</sub>), 25.4 (CH<sub>2</sub>), 24.6 (CH<sub>2</sub>), 24.5 (CH<sub>2</sub>), 22.6 (CH<sub>2</sub>), 14.0 (CH<sub>3</sub>) ppm; IR (neat):  $\tilde{\nu}_{\max}$  (cm<sup>-1</sup>) = 3327, 2926, 2854, 1681, 1614, 1521, 1412, 1365; HRMS (ESI):  $m/z$  calculated for C<sub>22</sub>H<sub>41</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup> 365.3163, found 365.3150.

**Synthesis of *N*-(*tert*-Butyl)-1-(2-(4-methoxyphenyl)acetyl)-4-pentyl-piperidine-2-carboxamide (6l):** Another 1.0 mmol aliquot of **5g** (153 mg, 1 equiv., see preparation of 6k) was then used in the U-3CR together with 4-methoxyphenylacetic acid (199 mg, 1.2 mmol, 1.2 equiv.) and *tert*-butyl isocyanide (135  $\mu$ L, 1.2 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (cyclohexane/EtOAc = 3:1) provided **6l** as a white solid (345 mg, 0.85 mmol, 85 %). Two rotamers were present on NMR-timescale in a 1:0.27 ratio. RF = 0.36 (cyclohexane/EtOAc = 2:1); m.p. 65–66 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  7.17 (d,  $J$  = 8.5 Hz, 2.54H), 6.85 (d,  $J$  = 8.5 Hz, 2.54H), 5.90 (bs, 1H), 5.26 (bs, 0.27H), 5.16 (d,  $J$  = 5.4 Hz, 1H), 4.63 (d,  $J$  = 13.2 Hz, 0.27H), 4.44 (d,  $J$  = 4.7 Hz, 0.27H), 3.74–3.67 (m, 7.35H), 4.63 (t,  $J$  = 13.2 Hz, 0.27H), 2.43 (m, 0.54H), 2.22 (d,  $J$  = 12.5 Hz, 1H), 1.78 (m, 1H), 1.64 (m, 2.27H), 1.42 (bs, 0.27H), 1.33–1.11 (m, 20.59H), 1.04 (m, 1.27H), 0.86 (m, 5.08H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz):  $\delta$  171.4 (C<sub>q</sub>), 171.2 (C<sub>q</sub>), 169.9 (C<sub>q</sub>), 168.2 (C<sub>q</sub>), 158.7 (C<sub>q</sub>), 158.5 (C<sub>q</sub>), 129.4 (CH), 129.4 (CH), 126.7 (C<sub>q</sub>), 126.5 (C<sub>q</sub>), 114.6 (CH), 114.3 (CH), 58.4 (CH), 55.3 (CH), 55.3 (CH<sub>3</sub>), 52.5 (CH<sub>3</sub>), 51.1 (C<sub>q</sub>), 50.9 (C<sub>q</sub>), 44.2 (CH<sub>2</sub>), 40.7 (CH<sub>2</sub>), 40.2 (CH<sub>2</sub>), 40.0 (CH<sub>2</sub>), 36.8 (CH<sub>2</sub>), 36.5 (CH<sub>2</sub>), 32.8 (CH<sub>2</sub>), 32.3 (CH), 32.1 (CH<sub>2</sub>), 32.0 (CH<sub>2</sub>), 31.9 (CH<sub>2</sub>), 31.7 (CH<sub>2</sub>), 31.6 (CH), 31.3 (CH<sub>2</sub>), 28.7 (CH<sub>3</sub>), 28.3 (CH<sub>3</sub>), 26.1 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 22.6 (CH<sub>2</sub>), 22.6 (CH<sub>2</sub>), 14.0 (CH<sub>3</sub>), 14.0 (CH<sub>3</sub>) ppm; IR (neat):  $\tilde{\nu}_{\max}$  (cm<sup>-1</sup>) = 3335, 2924, 1680, 1626, 1510, 1450, 1245, 1176, 1034, 640, 576, 530; HRMS (ESI):  $m/z$  calculated for C<sub>24</sub>H<sub>39</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup> 403.2955, found 403.2968.

**Synthesis of Methyl (4-Cyclopentyl-1-pivaloylpiperidine-2-carboxonyl)-glycinate (6m):** The general procedure IV with 0.57 g (3.0 mmol, 1 equiv.) of **4g** gave 0.39 g (2.55 mmol, 85 %) of 3,4,5,6-tetrahydro-4-cyclopentylpyridine **5h**. An 0.5 mmol aliquot of **5h** (76 mg, 1 equiv.) was then used in the U-3CR together with pivalic acid (61 mg, 0.6 mmol, 1.2 equiv.) and methyl isocynoacetate (55  $\mu$ L, 0.6 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (cyclohexane/EtOAc = 5:2) provided **6m** as a slowly crystallizing oil (109 mg, 0.31 mmol, 62 %). RF = 0.12 (cyclohexane/EtOAc = 4:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  6.68 (bs, 1H), 5.24 (bs, 1H), 4.21 (m, 2H), 3.80 (dd,  $J$  = 18.2, 4.2 Hz, 1H), 3.72 (s, 3H), 3.04 (t,  $J$  = 13.2 Hz, 1H), 2.37 (d,  $J$  = 13.2 Hz, 1H), 1.72–1.68 (m, 3H), 1.59 (m, 3H), 1.53–1.37 (m, 3H), 1.33 (s, 9H), 1.28–1.05 (m, 4H) ppm;

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz):  $\delta$  178.6 (C<sub>q</sub>), 171.7 (C<sub>q</sub>), 170.3 (C<sub>q</sub>), 52.3 (CH), 46.2 (CH<sub>3</sub>), 44.5 (CH<sub>2</sub>), 40.8 (CH<sub>2</sub>), 38.9 (C<sub>q</sub>), 37.6 (CH), 37.6 (CH), 31.0 (CH<sub>2</sub>), 30.9 (CH<sub>2</sub>), 30.2 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 28.3 (CH<sub>3</sub>), 25.3 (CH<sub>2</sub>), 25.2 (CH<sub>2</sub>) ppm; IR (neat):  $\tilde{\nu}_{\max}$  (cm<sup>-1</sup>) = 3356, 2949, 2868, 1753, 1680, 1618, 1516, 1412, 1366, 1201, 983, 536; HRMS (ESI):  $m/z$  calculated for C<sub>19</sub>H<sub>33</sub>N<sub>2</sub>O<sub>4</sub> [M + H]<sup>+</sup> 353.2435, found 353.2445.

**Synthesis of *N*-(*tert*-Butyl)-4-cyclopentyl-1-(2-(4-methoxyphenyl)acetyl)piperidine-2-carboxamide (6n):** Another 0.5 mmol aliquot of **5h** (76 mg, 1 equiv., see preparation of 6m) was then used in the U-3CR together with 4-methoxyphenylacetic acid (100 mg, 0.6 mmol, 1.2 equiv.) and *tert*-butyl isocyanide (62  $\mu$ L, 0.6 mmol, 1.2 equiv.) following the general procedure IV. Column chromatography (cyclohexane/EtOAc = 3:1) provided **6n** as a white solid (173 mg, 0.43 mmol, 86 %). Two rotamers were present on NMR-timescale in a 1:0.27 ratio. RF = 0.42 (cyclohexane/EtOAc = 2:1); m.p. 104 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  7.16 (d,  $J$  = 8.5 Hz, 2.54H), 7.84 (d,  $J$  = 8.5 Hz, 2.54H), 5.92 (bs, 1H), 5.23 (bs, 0.27H), 5.15 (d,  $J$  = 4.8 Hz, 1H), 4.61 (d,  $J$  = 13.4 Hz, 0.27H), 4.44 (bs, 0.27H), 3.85–3.66 (m, 7.35H), 2.91 (t,  $J$  = 13.2 Hz, 1H), 2.43 (m, 0.54H), 2.26 (d,  $J$  = 12.9 Hz, 1H), 1.78–1.31 (m, 12.7H), 1.22 (s, 9.27H), 1.13 (s, 2.43H), 1.11–1.02 (m, 2.27H), 1.00–0.90 (m, 1.27H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz):  $\delta$  171.4 (C<sub>q</sub>), 171.1 (C<sub>q</sub>), 170.0 (C<sub>q</sub>), 168.1 (C<sub>q</sub>), 158.6 (C<sub>q</sub>), 158.5 (C<sub>q</sub>), 129.4 (CH), 129.4 (CH), 126.7 (C<sub>q</sub>), 126.5 (C<sub>q</sub>), 114.5 (CH), 114.2 (CH), 58.3 (CH), 55.2 (CH), 55.2 (CH<sub>3</sub>), 52.4 (CH<sub>3</sub>), 51.1 (C<sub>q</sub>), 50.8 (C<sub>q</sub>), 46.1 (CH), 45.9 (CH), 44.2 (CH<sub>2</sub>), 40.7 (CH<sub>2</sub>), 40.2 (CH<sub>2</sub>), 39.9 (CH<sub>2</sub>), 37.9 (CH), 37.3 (CH), 31.8 (CH<sub>2</sub>), 31.0 (CH<sub>2</sub>), 30.7 (CH<sub>2</sub>), 30.3 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 29.6 (CH<sub>2</sub>), 28.6 (CH<sub>3</sub>), 28.3 (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 25.2 (CH<sub>2</sub>), 25.2 (CH<sub>2</sub>), 25.1 (CH<sub>2</sub>) ppm; IR (neat):  $\tilde{\nu}_{\max}$  (cm<sup>-1</sup>) = 3337, 2951, 2866, 1678, 1624, 1510, 1450, 1246, 1178, 1036, 910, 729, 646, 526; HRMS (ESI):  $m/z$  calculated for C<sub>24</sub>H<sub>37</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup> 401.2799, found 401.2813.

**Synthesis of 4-Cyclohexyl-*N*-pentyl-1-pivaloylpiperidine-2-carbox-amide (6o):** The general procedure IV with 0.61 g (3.0 mmol, 1 equiv.) of **4h** gave 0.46 g (2.76 mmol, 92 %) of 3,4,5,6-tetrahydro-4-cyclohexylpyridine **5i**. An 0.5 mmol aliquot of **5i** (83 mg, 1 equiv.) was then used in the U-3CR together with pivalic acid (61 mg, 0.6 mmol, 1.2 equiv.) and pentyl isocyanide (78  $\mu$ L, 0.6 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (cyclohexane/EtOAc = 4:1) provided **6o** as a white solid (138 mg, 0.38 mmol, 76 %). RF = 0.31 (cyclohexane/EtOAc = 4:1); m.p. 108 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  6.19 (bs, 1H), 5.11 (bs, 1H), 4.18 (bs, 1H), 3.25 (m, 1H), 3.11 (m, 1H), 2.89 (m, 1H), 2.29 (d,  $J$  = 12.0 Hz, 1H), 1.76–1.59 (m, 1H), 1.42 (m, 2H), 1.27 (s, 9H), 1.26–0.90 (m, 12H), 0.87 (t,  $J$  = 7.0 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz):  $\delta$  178.2 (C<sub>q</sub>), 171.1 (C<sub>q</sub>), 44.4 (CH), 42.5 (CH), 39.1 (CH<sub>2</sub>), 38.8 (C<sub>q</sub>), 37.0 (CH), 29.9 (CH<sub>2</sub>), 29.6 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 29.0 (CH<sub>2</sub>), 28.8 (CH<sub>2</sub>), 28.2 (CH<sub>3</sub>), 26.6 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>), 22.2 (CH<sub>2</sub>), 13.9 (CH<sub>3</sub>) ppm; IR (neat):  $\tilde{\nu}_{\max}$  (cm<sup>-1</sup>) = 3329, 2922, 2851, 1664, 1612, 1522, 1412, 1165, 997, 922, 731, 629, 532; HRMS (ESI):  $m/z$  calculated for C<sub>22</sub>H<sub>41</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup> 365.3163, found 365.3173.

**Synthesis of *N*-(*tert*-Butyl)-4-cyclohexyl-1-(pent-4-enoyl)piperidine-2-carboxamide (6p):** Another 0.5 mmol aliquot of **5i** (83 mg, 1 equiv., see preparation of 6o) was then used in the U-3CR together with 4-pentenoic acid (62  $\mu$ L, 0.6 mmol, 1.2 equiv.) and *tert*-butyl isocyanide (62  $\mu$ L, 0.6 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (cyclohexane/EtOAc = 4:1) provided **6p** as a white solid (155 mg, 0.44 mmol, 89 %). Two rotamers were present on NMR-timescale in a 1:0.21 ratio. RF = 0.30 (cyclohexane/EtOAc = 4:1); m.p. 140 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  5.96 (bs, 1H), 5.84 (m, 1.21H), 5.70 (bs, 0.21H), 5.14 (d,  $J$  = 4.5 Hz, 1H), 5.05 (d,  $J$  = 17.1 Hz, 1.21H), 4.99 (d,  $J$  = 10.1 Hz, 1.21H), 4.65 (d,  $J$  = 12.9 Hz, 0.21H), 4.40 (bs, 0.21H), 3.79 (d,  $J$  = 13.3 Hz, 1H), 3.04 (dt,



$J = 13.2, 1.5 \text{ Hz, 1H}$ ), 2.54–2.31 (m, 5.26H), 2.19 (d,  $J = 14.1 \text{ Hz, 1H}$ ), 1.77–1.56 (m, 8.47H), 1.32 (s, 1.89H), 1.28 (s, 9H), 1.124–0.81 (m, 9.68H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  172.3 ( $\text{C}_q$ ), 171.9 ( $\text{C}_q$ ), 170.3 ( $\text{C}_q$ ), 168.7 ( $\text{C}_q$ ), 137.1 (CH), 137.0 (CH), 115.6 ( $\text{CH}_2$ ), 115.4 ( $\text{CH}_2$ ), 57.8 (CH), 52.6 (CH), 51.5 ( $\text{C}_q$ ), 50.9 ( $\text{C}_q$ ), 43.7 ( $\text{CH}_2$ ), 42.5 (CH), 42.2 (CH), 40.0 ( $\text{CH}_2$ ), 37.7 (CH), 36.8 (CH), 32.6 ( $\text{CH}_2$ ), 32.5 ( $\text{CH}_2$ ), 30.2 ( $\text{CH}_2$ ), 29.9 ( $\text{CH}_2$ ), 29.6 ( $\text{CH}_2$ ), 29.6 ( $\text{CH}_2$ ), 29.5 ( $\text{CH}_2$ ), 29.2 ( $\text{CH}_2$ ), 29.1 ( $\text{CH}_2$ ), 29.0 ( $\text{CH}_2$ ), 28.7 ( $\text{CH}_3$ ), 28.7 ( $\text{CH}_3$ ), 28.2 ( $\text{CH}_2$ ), 26.6 ( $\text{CH}_2$ ), 26.6 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ), 26.4 ( $\text{CH}_2$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3335, 2922, 2851, 1682, 1627, 1535, 1448, 1425, 1364, 1259, 1224, 999, 910, 730, 644, 403; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{21}\text{H}_{37}\text{N}_2\text{O}_2$  [ $\text{M} + \text{H}$ ] $^+$  349.2850, found 349.2857.

**Synthesis of 1-Acetyl-*N*-(*tert*-butyl)-4-phenylpiperidine-2-carboxamide (6q):** The general procedure IV with 0.97 g (6.0 mmol, 1 equiv.) of commercial 4-phenylpiperidine gave 0.91 g (5.72 mmol, 95 %) of 3,4,5,6-tetrahydro-4-phenylpyridine **5j**. An 0.35 mmol aliquot of **5j** (56 mg, 1 equiv.) was then used in the U-3CR together with acetic acid (24  $\mu\text{L}$ , 0.42 mmol, 1.2 equiv.) and *tert*-butyl isocyanide (48  $\mu\text{L}$ , 0.42 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (EtOAc) provided **6q** as a white solid (101 mg, 0.33 mmol, 95 %). Two rotamers were present on NMR-timescale in a 1:0.18 ratio. RF = 0.30 (EtOAc);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.34–7.20 (m, 5.90H), 6.07 (bs, 1H), 5.82 (bs, 0.18H), 5.25 (d,  $J = 5.5 \text{ Hz, 1H}$ ), 4.81 (d,  $J = 13.5 \text{ Hz, 0.18H}$ ), 4.47 (d,  $J = 5.0 \text{ Hz, 0.18H}$ ), 3.87 (d,  $J = 13.5 \text{ Hz, 1H}$ ), 3.35 (dt,  $J = 13.0, 2.5 \text{ Hz, 1H}$ ), 3.25 (tt,  $J = 12.5, 3.5 \text{ Hz, 1H}$ ), 2.75 (m, 0.56), 2.37 (m, 1H), 2.22 (s, 3H), 2.18 (s, 0.56H), 1.92 (m, 1.18H), 1.72–1.60 (m, 2.36H), 1.41 (s, 1.62H), 1.36 (s, 9H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  170.7 ( $\text{C}_q$ ), 170.3 ( $\text{C}_q$ ), 170.0 ( $\text{C}_q$ ), 168.3 ( $\text{C}_q$ ), 145.2 ( $\text{C}_q$ ), 144.6 ( $\text{C}_q$ ), 128.5 (CH), 128.5 (CH), 126.8 (CH), 126.7 (CH), 126.5 (CH), 126.4 (CH), 58.7 (CH), 52.4 (CH), 51.7 ( $\text{C}_q$ ), 51.0 ( $\text{C}_q$ ), 44.4 ( $\text{CH}_2$ ), 39.7 ( $\text{CH}_2$ ), 38.4 (CH), 37.6 ( $\text{CH}_3$ ), 34.0 ( $\text{CH}_2$ ), 33.0 ( $\text{CH}_2$ ), 32.6 ( $\text{CH}_2$ ), 31.6 ( $\text{CH}_2$ ), 28.9 ( $\text{CH}_3$ ), 28.8 ( $\text{CH}_3$ ), 21.7 ( $\text{CH}_3$ ), 21.7 ( $\text{CH}_3$ ) ppm. IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3317, 2966, 1678, 1627, 1533, 1421, 1364, 1256, 1225, 729, 698; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{18}\text{H}_{26}\text{N}_2\text{NaO}_2$  [ $\text{M} + \text{Na}$ ] $^+$  325.1886, found 325.1901. A single crystal suitable for X-ray diffraction was grown from a dichloromethane/pentane mixture. CCDC 1910686 (for compound **6q**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

**Synthesis of 1-Acetyl-*N*-cyclohexyl-4-phenylpiperidine-2-carboxamide (6r):** Another 0.35 mmol aliquot of **5j** (56 mg, 1 equiv., see preparation of **6q**) was then used in the U-3CR together with acetic acid (24  $\mu\text{L}$ , 0.42 mmol, 1.2 equiv.) and cyclohexyl isocyanide (52  $\mu\text{L}$ , 0.42 mmol, 1.2 equiv.) following the general procedure IV. Flash chromatography (EtOAc) provided **6r** as a white solid (103 mg, 0.31 mmol, 90 %). Two rotamers were present on NMR-timescale in a 1:0.24 ratio. RF = 0.40 (EtOAc);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.34–7.18 (m, 6.20H), 6.11 (d,  $J = 7.5 \text{ Hz, 1H}$ ), 6.05 (d,  $J = 8.5 \text{ Hz, 0.24H}$ ), 5.29 (d,  $J = 5.5 \text{ Hz, 1H}$ ), 4.78 (d,  $J = 13.5 \text{ Hz, 0.24H}$ ), 4.51 (d,  $J = 5.5 \text{ Hz, 0.24H}$ ), 3.85 (d,  $J = 13.5 \text{ Hz, 1H}$ ), 3.76 (m, 1.24H), 3.33 (dt,  $J = 13.0, 2.5 \text{ Hz, 1H}$ ), 3.20 (tt,  $J = 12.5, 3.5 \text{ Hz, 1H}$ ), 2.72 (m, 0.72), 2.38 (m, 1H), 2.20 (s, 3H), 2.16 (s, 0.72H), 1.97–1.80 (m, 3.72H), 1.77–1.56 (m, 6.2H), 1.42–1.30 (m, 2.48H), 1.23–1.10 (m, 3.72H) ppm.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  170.7 ( $\text{C}_q$ ), 170.3 ( $\text{C}_q$ ), 169.7 ( $\text{C}_q$ ), 167.9 ( $\text{C}_q$ ), 145.1 ( $\text{C}_q$ ), 144.5 ( $\text{C}_q$ ), 128.5 (CH), 128.5 (CH), 126.7 (CH), 126.7 (CH), 126.5 (CH), 126.4 (CH), 58.3 (CH), 51.9 (CH), 48.7 (CH), 48.0 (CH), 44.4 ( $\text{CH}_2$ ), 39.6 ( $\text{CH}_2$ ), 38.4 (CH), 37.7 (CH), 33.1 ( $\text{CH}_2$ ), 33.0 ( $\text{CH}_2$ ), 32.8 ( $\text{CH}_2$ ), 32.5 ( $\text{CH}_2$ ), 25.4 ( $\text{CH}_2$ ), 25.3 ( $\text{CH}_2$ ), 24.9 ( $\text{CH}_2$ ), 24.7 ( $\text{CH}_2$ ), 21.8 ( $\text{CH}_3$ ), 21.7 ( $\text{CH}_3$ ) ppm. IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3300, 2930, 2854, 1631, 1527, 1421, 730, 633, 534, 496; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{NaO}_2$  [ $\text{M} + \text{Na}$ ] $^+$  351.2043, found 351.2058.

### Synthesis of Argatroban (3)

***N*ω,*N*ω'-Bis((benzyloxy)carbonyl)-*N*2-((3-methylquinolin-8-yl)sulfonyl)-*L*-arginine (8b):** TFA (65 mL) was added to a solution of **21** (Boc-Arg(Cbz) $_2$ -OH; 2.5 g, 4.61 mmol, 1 equiv.) in  $\text{CH}_2\text{Cl}_2$  (65 mL) at 0 °C. The reaction mixture was stirred for 1 h at this temperature and then concentrated under reduced pressure. The resulting residue was co-evaporated two times with toluene to furnish an off-white foamy solid. The residue was redissolved into a 2:1 mixture of THF and  $\text{H}_2\text{O}$  (120 mL) and DIPEA (4.00 mL, 23.0 mmol, 5 equiv.) was added. Then, the resulting solution was cooled to 0 °C and **22** (3-methylquinoline-8-sulfonyl chloride; 1.34 g, 5.53 mmol, 1.2 equiv.) was added portion wise. After complete addition, the reaction mixture was warmed to room temperature and stirred for 16 h. Next, EtOAc was added (50 mL) and the layers were separated. The water layer was extracted with ethyl acetate (2  $\times$  50 mL) and the combined layers were washed with saturated  $\text{NH}_4\text{Cl}$ (aq.) and Brine, dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/EtOAc = 1:4) to obtain **8b** as a white foamy solid (2.94 g, 4.54 mmol, 98 %). RF = 0.20 (cyclohexane/EtOAc = 1:4); m.p. 160 °C;  $[\alpha]_{\text{D}}^{20} + 80^\circ$  (c = 1.00,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  9.36 (bs, 1H), 9.27 (bs, 1H), 8.78 (s, 1H), 8.26 (d,  $J = 7.0 \text{ Hz, 1H}$ ), 7.92 (s, 1H), 7.88 (d,  $J = 8.0 \text{ Hz, 1H}$ ), 7.48 (t,  $J = 7.5 \text{ Hz, 1H}$ ), 7.42–7.35 (m, 5H), 7.26–7.14 (m, 5H), 5.23 (s, 2H), 4.94 (d,  $J = 12.5 \text{ Hz, 1H}$ ), 4.81 (d,  $J = 12.5 \text{ Hz, 1H}$ ), 4.24 (bs, 1H), 3.91 (m, 2H), 2.46 (s, 3H), 1.89–1.61 (m, 4H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  174.1 ( $\text{C}_q$ ), 163.3 ( $\text{C}_q$ ), 160.5 ( $\text{C}_q$ ), 155.7 ( $\text{C}_q$ ), 153.0 (CH), 141.1 ( $\text{C}_q$ ), 136.5 ( $\text{C}_q$ ), 136.0 ( $\text{C}_q$ ), 125.6 (CH), 134.5 ( $\text{C}_q$ ), 132.9 (CH), 132.1 ( $\text{C}_q$ ), 129.9 (CH), 128.8 (CH), 128.6 ( $\text{C}_q$ ), 128.4 (CH), 128.3 (CH), 127.7 (CH), 127.5 (CH), 125.3 (CH), 69.0 ( $\text{CH}_2$ ), 66.7 ( $\text{CH}_2$ ), 55.9 (CH), 29.2 ( $\text{CH}_2$ ), 24.3 ( $\text{CH}_2$ ), 18.6 ( $\text{CH}_3$ ) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 2986, 2363, 1717, 1607, 1508, 1240, 1161, 1095, 696, 584; HRMS (ESI):  $m/z$  calculated for  $\text{C}_{23}\text{H}_{34}\text{N}_5\text{O}_8\text{S}$  [ $\text{M} + \text{H}$ ] $^+$  648.2123, found 648.2121.

**1-(*N*ω,*N*ω'-Bis(1-(benzyloxy)carbonyl)-*N*2-((3-methylquinolin-8-yl)sulfonyl)-*L*-arginyl)-*N*-(6-bromopyridin-2-yl)-4-methylpiperidine-2-carboxamide (9b):** Tetrahydro-4-methyl pyridine **5a** (146 mg, 1.50 mmol, 1.0 equiv.), obtained quantitatively from commercial 4-methyl piperidine using the general procedure IV, was dissolved in TFE (10 mL). Then, amino acid **8b** (1.46 g, 2.25 mmol, 1.5 equiv.) and 2-bromo-6-isocyanopyridine<sup>[30]</sup> (**7**; 329 mg, 1.80 mmol, 1.20 equiv.) were added sequentially. After 48 h the mixture was concentrated in vacuo and purified using flash chromatography (cyclohexane/EtOAc = 4:1) to yield an off-white foam (902 mg, 0.97 mmol, 65 %). The product is a 1:1 mixture of diastereoisomers. NMR-analysis displays rotamers of which the major signals are reported  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  9.45 (bs, 2H), 9.28 (bs, 2H), 8.92 (s, 1H), 8.82 (s, 2H), 8.33 (d,  $J = 7.0 \text{ Hz, 1H}$ ), 8.24 (d,  $J = 7.5 \text{ Hz, 1H}$ ), 8.03–7.90 (m, 4H), 7.78 (s, 1H), 7.74 (s, 1H), 7.70 (d,  $J = 7.0 \text{ Hz, 1H}$ ), 7.56 (t,  $J = 8.0 \text{ Hz, 1H}$ ), 7.52 (t,  $J = 8.0 \text{ Hz, 1H}$ ), 7.49–7.25 (m, 21H), 7.14 (m, 2H), 5.30–5.04 (m, 8H), 4.79 (d,  $J = 5.5 \text{ Hz, 1H}$ ), 4.72 (m, 1H), 4.50 (m, 1H), 4.46 (d,  $J = 5.5 \text{ Hz, 1H}$ ), 4.08–3.93 (m, 4H), 3.70 (d,  $J = 13.5 \text{ Hz, 1H}$ ), 3.65 (d,  $J = 13.5 \text{ Hz, 1H}$ ), 3.04 (dt,  $J = 13.0, 2.0 \text{ Hz, 1H}$ ), 2.95 (dt,  $J = 13.0, 2.0 \text{ Hz, 1H}$ ), 2.95 (s, 3H), 2.40 (s, 3H), 1.95 (d,  $J = 14.0 \text{ Hz, 1H}$ ), 1.89–1.50 (m, 12H), 1.40 (d,  $J = 12.5 \text{ Hz, 1H}$ ), 0.92 (m, 2H), 0.82 (d,  $J = 6.5 \text{ Hz, 3H}$ ), 0.80 (d,  $J = 6.5 \text{ Hz, 3H}$ ), 0.63 (dq,  $J = 12.5, 4.0 \text{ Hz, 1H}$ ), 0.37 (dt,  $J = 13.0, 6.0 \text{ Hz, 1H}$ ) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  171.4 ( $\text{C}_q$ ), 171.1 ( $\text{C}_q$ ), 168.8 ( $\text{C}_q$ ), 168.7 ( $\text{C}_q$ ), 163.8 ( $\text{C}_q$ ), 163.7 ( $\text{C}_q$ ), 160.5 ( $\text{C}_q$ ), 160.5 ( $\text{C}_q$ ), 155.8 ( $\text{C}_q$ ), 155.8 ( $\text{C}_q$ ), 153.3 (CH), 152.7 (CH), 150.8 ( $\text{C}_q$ ), 150.7 ( $\text{C}_q$ ), 141.5 ( $\text{C}_q$ ), 141.4 ( $\text{C}_q$ ), 140.3 (CH), 140.1 (CH), 139.3 ( $\text{C}_q$ ), 139.2 ( $\text{C}_q$ ), 136.8 ( $\text{C}_q$ ), 136.8 ( $\text{C}_q$ ), 136.8 ( $\text{C}_q$ ), 135.2 (CH), 135.0 (CH), 134.7 ( $\text{C}_q$ ), 134.6 ( $\text{C}_q$ ), 132.7 (CH), 132.6 (CH), 132.2 (CH), 131.7 (CH), 128.8 (CH), 128.8 (CH), 128.8 (CH), 128.8 (CH), 128.7 (CH), 128.7 (CH), 128.5 (CH), 128.5 ( $\text{C}_q$ ), 128.4



(CH), 128.4 (C<sub>q</sub>), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 125.3 (CH), 125.1 (CH), 123.7 (CH), 123.6 (CH), 112.4 (CH), 112.0 (CH), 69.0 (CH<sub>2</sub>), 68.9 (CH<sub>2</sub>), 66.9 (CH<sub>2</sub>), 66.9 (CH<sub>2</sub>), 54.1 (CH), 53.3 (CH), 53.0 (CH), 52.8 (CH), 44.0 (CH<sub>2</sub>), 43.9 (CH<sub>2</sub>), 43.6 (CH<sub>2</sub>), 43.3 (CH<sub>2</sub>), 33.6 (CH<sub>2</sub>), 33.5 (CH<sub>2</sub>), 33.1 (CH<sub>2</sub>), 33.0 (CH<sub>2</sub>), 30.8 (CH<sub>2</sub>), 30.4 (CH<sub>2</sub>), 26.5 (CH), 26.3 (CH), 24.7 (CH<sub>2</sub>), 24.5 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>), 18.8 (CH<sub>3</sub>), 18.7 (CH<sub>3</sub>) ppm; IR (neat):  $\tilde{\nu}_{\text{max}}$  (cm<sup>-1</sup>) = 1717, 1604, 1564, 1508, 1431, 1384, 1223, 1155, 1090, 696, 581; HRMS (ESI): *m/z* calculated for C<sub>44</sub>H<sub>48</sub>BrN<sub>8</sub>O<sub>8</sub>S [M + H]<sup>+</sup> 927.2494, found 927.2510.

**4-Methyl-1-(((3-Methyl-1,2,3,4-tetrahydroquinolin-8-yl)sulfonyl)-L-arginyl)piperidine-2-carboxylic Acid (Argatroban, 3):** U-3CR product **9b** (186 mg, 0.20 mmol, 1.0 equiv.) was dissolved into ethanol (2 mL) and aqueous NaOH (2 M, 1.0 mL, 2.0 mmol, 10 equiv.) was added dropwise to the solution. The resulting mixture was heated to reflux and stirred for 1 hour. The mixture was cooled to room temperature and CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added. The water layer was acidified to pH 2 with an aqueous HCl solution (2 M) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 ×). The collected organic fractions were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was further purified using flash chromatography (EtOAc/iPrOH/H<sub>2</sub>O = 5:2:0.25) to yield an off-white powder (120 mg, 0.188 mmol, 94 %). The resulting product is a mixture of two diastereoisomers of the hydrolyzed (2*R*,4*R*)-1-(*N*ω'-((benzyloxy)carbonyl)-N2-((3-methylquinolin-8-yl)sulfonyl)-L-arginyl)-4-methylpiperidine-2-carboxylic acid as well as the derivative with the second Cbz-group partially cleaved. RF = 0.75 (EtOAc/iPrOH/H<sub>2</sub>O = 4:2:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 8.93 (s, 1H), 8.31 (d, *J* = 6.5 Hz, 1H), 8.15 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.45–7.36 (m, 5H), 5.22 (s, 1H), 4.44–4.36 (m, 2H), 3.85 (d, *J* = 12.5 Hz, 1H), 3.38–3.12 (m, 3H), 2.58 (s, 1H), 2.10 (m, 1H), 1.78–1.45 (m, 6H), 0.88 (m, 1H), 0.79 (d, *J* = 6.0 Hz, 3H), 0.67 (m, 1H) ppm. HRMS (ESI): *m/z* calculated for C<sub>31</sub>H<sub>44</sub>N<sub>6</sub>O<sub>7</sub>S [M + H]<sup>+</sup> 639.2595, found 639.2581. Then, 32 mg of this material (0.05 mmol, 1.0 equiv.) was dissolved in a 1:1 mixture of ethanol and acetic acid (5 mL) and Pd/C (10 w/w %, 6 mg, 0.005 mmol, 0.1 equiv.) was added. The reaction flask was exposed to an atmospheric pressure of H<sub>2</sub> and stirred for 16 h at r.t. Then, the suspension was filtered through Celite, concentrated in vacuo and purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH = 80:20) to yield the title compound as a white solid (22 mg, 0.044 mmol, 88 %). The product is available as a 1:1 mixture of diastereoisomers.

The reaction was repeated with the single diastereoisomer obtained by SFC separation on 2.5 mg scale. Argatroban (3, 2 mg) was obtained as a mixture of two epimers at the quinoline ring in a 36:64 ratio. <sup>1</sup>H NMR (MeOD, 500 MHz): δ 7.44 (d, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 6.55 (t, *J* = 6.5 Hz, 1H), 4.63 (bs, 2H), 4.13 (m, 2H), 4.00 (m, 1H), 3.43 (m, 1H), 3.22–2.68 (m, 5H), 2.43 (m, 1H), 2.15 (m, 1H), 1.99 (m, 1H), 1.69 (m, 3H), 1.48 (m, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 0.70 (m, 1H), 0.88 (d, *J* = 5.5 Hz, 3H), 0.65 (m, 1H) ppm; <sup>13</sup>C NMR (MeOD, 125 MHz): δ 177.4 (C<sub>q</sub>), 171.4 (C<sub>q</sub>), 158.6 (C<sub>q</sub>), 144.2 (C<sub>q</sub>), 135.3 (CH), 128.9 (CH), 124.5 (C<sub>q</sub>), 119.6 (C<sub>q</sub>), 115.7 (CH), 59.6 (CH), 53.1 (CH), 49.1 (CH<sub>2</sub>), 41.5 (CH<sub>2</sub>), 41.0 (CH<sub>2</sub>), 37.5 (CH<sub>2</sub>), 37.1 (CH<sub>2</sub>), 34.2 (CH<sub>2</sub>), 30.5 (CH<sub>2</sub>), 28.8 (CH), 27.0 (CH), 25.0 (CH<sub>2</sub>), 22.3 (CH<sub>3</sub>), 19.0 (CH<sub>3</sub>) ppm; HRMS (ESI): *m/z* calculated for C<sub>23</sub>H<sub>37</sub>N<sub>6</sub>O<sub>5</sub>S [M + H]<sup>+</sup> 509.2541, found 509.2525, which is in agreement with spectroscopic data of **3** from literature.<sup>[41–43]</sup>

## Acknowledgments

We thank Elwin Janssen for technical assistance, Jurriën Collet for HRMS measurements (both VU Amsterdam). We gratefully

thank Mercachem B.V. for separation of the diastereomers of **9b**. The research leading to these results has received funding from the Innovative Medicines Initiative Joint Undertaking project CHEM21 under Grant Agreement No. 115360, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/ 2007–2013) and EFPIA companies' in kind contribution. We thank Matthias Zeller (Youngstown State University) for collection of the X-ray diffraction data. The X-ray diffractometer was funded by NSF Grant 0087210, Ohio Board of Regents Grant CAP-491, and by Youngstown State University.

**Keywords:** Multicomponent reactions · Stereoselectivity · Pipecolic amides · Pharmaceuticals · Argatroban

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Received: February 11, 2019